REPORT DOCUMENTATION PAGE			
1. Recipient's Reference	**2. Originator's Reference** AGARD-AG-270(E)	**3. Further Reference** ISBN 92-835-1555-2	**4. Security Classification of Document** UNCLASSIFIED
5. Originator	Advisory Group for Aerospace Research and Development North Atlantic Treaty Organization 7 rue Ancelle, 92200 Neuilly sur Seine, France		
6. Title	SLEEP AND WAKEFULNESS: HANDBOOK FOR FLIGHT MEDICAL OFFICERS — SECOND EDITION		
7. Presented at			
8. Author(s)/Editor(s)	Group Captain A.N.Nicholson, OBE, RAF Barbara M.Stone		**9. Date** July 1987
10. Author's/Editor's Address	Royal Air Force Institute of Aviation Medicine Farnborough, Hampshire United Kingdom		**11. Pages** 74
12. Distribution Statement	This document is distributed in accordance with AGARD policies and regulations, which are outlined on the Outside Back Covers of all AGARD publications.		

13. Keywords/Descriptors

Sleep and wakefulness	Disturbed sleep
Sleep disorders	Transport operations
Circadian rhythms	Sustained performance
Hypnotics	

14. Abstract

This handbook was first published in 1982, and since then the understanding of sleep and wakefulness has advanced considerably. This new handbook emphasises the management of aircrew and the problems they experience in coping with irregularity of rest and activity.

This publication was sponsored by the Aerospace Medical Panel of AGARD.

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by
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and
B.M.Stone

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ADVISORY GROUP FOR AEROSPACE RESEARCH
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and

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Published July 1987

ISBN 92-835-1555-2

Printed by Specialised Printing Services Limited
40 Chigwell Lane, Loughton, Essex IG10 3TZ

PREFACE

This handbook was first published in 1982, and since then our understanding of sleep and wakefulness has advanced considerably. It is, therefore, opportune that a new handbook should now be published, and in preparing this edition we have been able to shift the emphasis much more toward the management of aircrew, and the problems they experience in coping with irregularity of rest and activity.

Once again we are indebted to our colleagues who have made so many contributions to the topics covered by this handbook. In particular, Michel Billiard (Montpelier), Roger Broughton (Ottawa), Giorgio Coccagna (Bologna), Charles Czeisler (Boston), William Dement (Stanford), Christian Guilleminault (Stanford), Bryce Hartman (San Antonio), Peter Hauri (Dartmouth), Laverne Johnson (San Diego), Karl Klein (Cologne), Paul Naitoh (San Diego), Alain Reinberg (Paris), Thomas Roth (Detroit), Michael Spencer (Farnborough) and Hans Wegmann (Cologne). We have drawn extensively from their writings and from their observations,. and are pleased to pay tribute to their work.

We also acknowledge the support of the Advisory Group for Aerospace Research and Development in this venture, and we hope that the handbook will be of help to medical officers in their approach to operational problems and in their management of aircrew.

We are grateful to Mrs Janet James who prepared the manuscript.

CONTENTS

CHAPTER 1

SLEEP AND WAKEFULNESS

Disturbed sleep is frequently experienced by personnel involved in air operations, and understanding the way in which sleep and wakefulness may be altered is specially important in the practice of aviation medicine. To this end, some knowledge of the sleep-wakefulness continuum and the circadian basis of the regular alternation of sleep and wakefulness is necessary, but, though changes in sleep associated with air operations are likely to be of primary interest, it must also be realised that the sleep of aircrew may be impaired for other reasons. In this context some familiarity with sleep disorders is useful. Further, every doctor concerned with the management of aircrew has been faced with the question of whether or not to use hypnotics, and an understanding of their clinical pharmacology is appropriate to ensure that these drugs are used wisely, and that adverse effects on subsequent performance are avoided. With this background the aeromedical practitioner will be able to deal confidently with the sleep problems of aircrew.

SLEEP ELECTROENCEPHALOGRAPHY

In general, studies on sleep in man are carried out in purpose-built sleep laboratories where the electroencephalogram, electromyogram and electro-oculogram are recorded. In many centres these studies are linked to assessments of alertness and performance. In the assessment of sleep disorders recordings of respiratory rate and airflow, together with oxymetry and myography of the anterior tibialis muscles, may also be needed. Over the years this approach has built up our present day knowledge of sleep and its disorders, and of unusual patterns of work and rest.

When only one channel is used for electroencephalographic recording the C4-A1 or C3-A2 derivation is recommended, and since electrical patterns from homologous areas are generally synchronous, either the right or left side may be selected. An additional channel, such as O_zP_z -O_3 or O_1A_2, helps in the definition of particular stages of sleep, and is also useful when artifacts or electrode failure occur. In particular, alpha rhythm is better recorded from occipital areas than from a single vertex channel. Electrode placements used in sleep recording are shown in Figure 1.

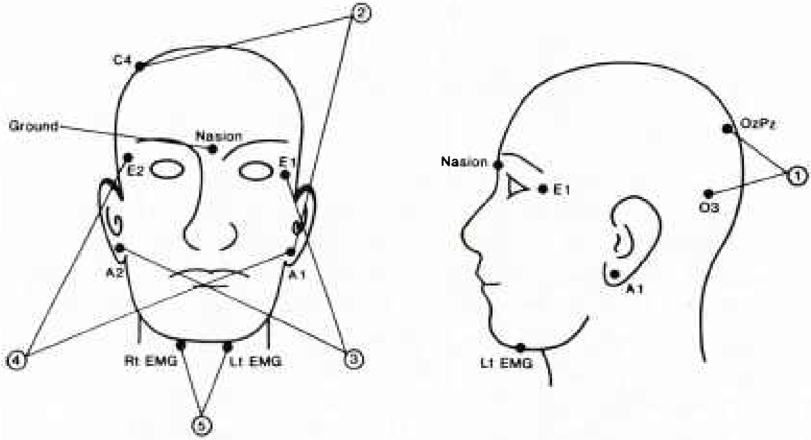

Fig.1 Electrode placements used in sleep recordings.

The eye movements seen in rapid eye movement (REM) sleep are differentiated from other similar signals, by using two channels of electro-oculography. The reference electrode is the same for both eyes, and this arrangement produces out of phase deflections. Artefacts usually register as in-phase deflections or are seen on one channel only. The submental electromyogram is also used in the definition of rapid eye movement sleep, as during rapid eye movement sleep electromyographic activity is at a relatively low level.

STAGES OF SLEEP

Information from the electroencephalogram, electro-oculogram and electromyogram is used to define the various sleep stages which appear during the night. Records are read in epochs, usually of 30 seconds duration, and with a paper speed of 10 mm per sec — this corresponds to a page of 30 cm length. Each epoch is assigned to a single stage, although it is not considered in isolation. There are many occasions when the score depends on the features of the preceding and succeeding epochs. When more than one stage is present, the one which takes up the greater portion is selected, and when more than half the tracing is obscured by muscle tension or amplifier blocking artefacts associated with movement of the subject the epoch is scored as movement.

Wakefulness is characterised by alpha and/or a low voltage mixed frequency activity. Some subjects have virtually a continuous

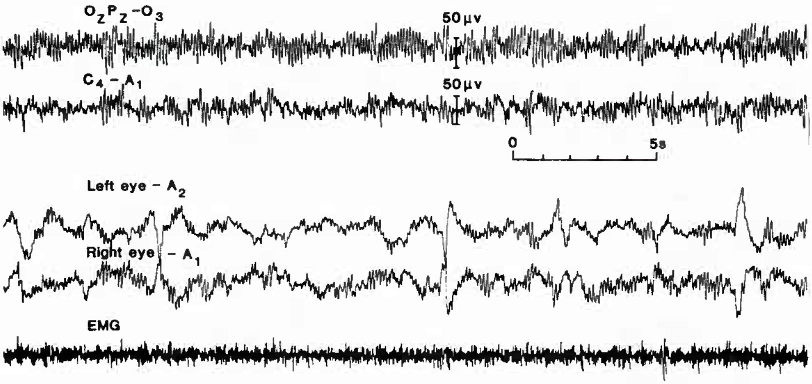

Fig.2 Wakefulness with continuous alpha activity.

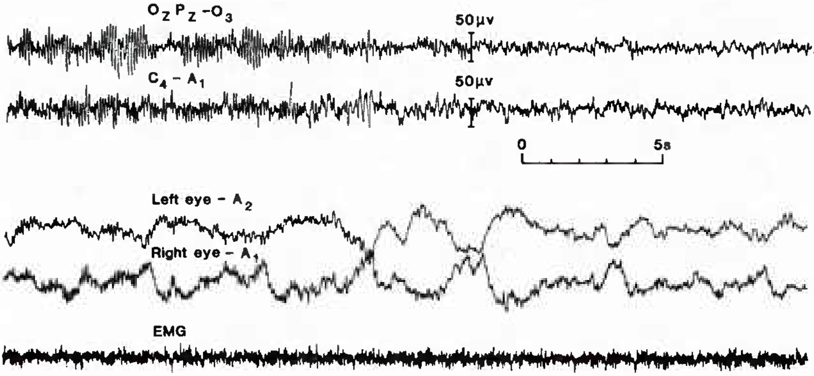

Fig.3 Transition from the alpha activity of wakefulness to drowsy (stage 1) sleep with rolling eye movements.

alpha record when their eyes are closed (Figure 2), while others may show little or none. This stage is usually, but not necessarily, accompanied by a relatively high amplitude electromyogram together with blinks and eye movements. The change from waking to drowsy (stage 1) sleep is associated with a general slowing of activity and by a decrease in the amount, amplitude and frequency of the alpha rhythm (Figure 3). The epoch is scored as stage 1 (drowsy) sleep when alpha activity together with low voltage activity amounts to less than 50% of the record, and is replaced by mixed frequency activity (Figure 4).

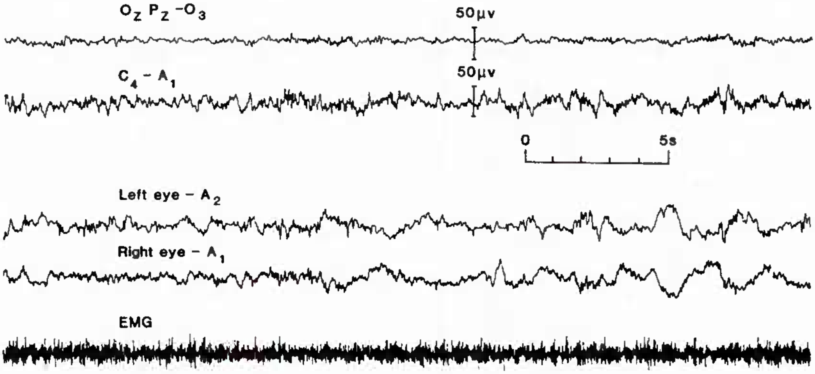

Fig.4 Drowsy (stage 1) sleep.

The relatively low voltage, mixed frequency electro-encephalogram characteristic of drowsy sleep has most activity in the 2-7 Hz range. The fast frequencies are of lower voltage than the 2-7 Hz activity. Stage 1 sleep occurs in the transition from wakefulness to sleep and with body movements. During nocturnal sleep it is usually of short duration — about 1 to 7 minutes, and in the latter part 7 Hz activity of high voltage (about 50-75 µv) may occur in irregularly spaced bursts, and vertex sharp waves may also appear. The amplitude of the vertex sharp wave is occasionally as high as 200 µv.

Traces of low voltage activity of 12-14 Hz may begin to appear as stage 2 sleep (sleep onset) approaches, but a rhythmic burst of at least 0.5 seconds duration (a sleep spindle) is necessary for the record to be scored as stage 2 sleep. In stage 1 sleep, particularly after wakefulness, there are slow eye movements, each of several seconds duration, which are usually most prominent during the early part of the stage. Rapid eye movements are absent, and the amplitude of the electromyogram is usually lower than during relaxed wakefulness.

Stage 2 sleep is scored when spindles and K complexes are present, and when there is insufficient high amplitude, slow activity for slow wave sleep (Figure 5). The initial appearance of spindles and/or K complexes signals the onset of sleep. A sleep spindle must last for at least 0.5 seconds and should consist of at least 6 to 7 distinct waves of 12-14 Hz. K complexes are waveforms which have a well defined negative sharp wave followed immediately by a

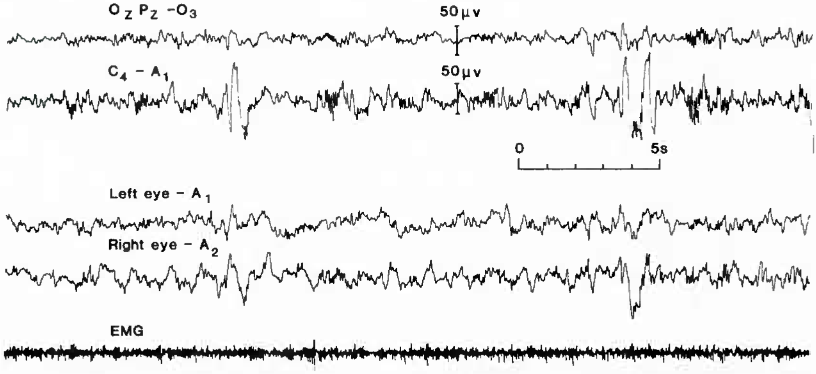

Fig.5 Stage 2 sleep.

positive component. The total duration exceeds 0.5 sec and waves of 12-14 Hz may or may not constitute a part of the complex. K complexes can occur as a response to sudden stimuli, but they appear frequently in the absence of any obvious stimulus.

A record in which at least 20%, but not more than 50%, of the epoch consists of waves of 2 Hz or slower (delta waves) with amplitudes greater than 75 µv from peak to peak (the difference between the most negative and positive points of the wave) is scored as stage 3. Wave by wave measurements are only necessary for epochs with borderline amounts (around 20 and 50%) of high amplitude, slow wave activity. Sleep spindes may or may not be present in stage 3 (Figure 6). When more than 50% of the epoch

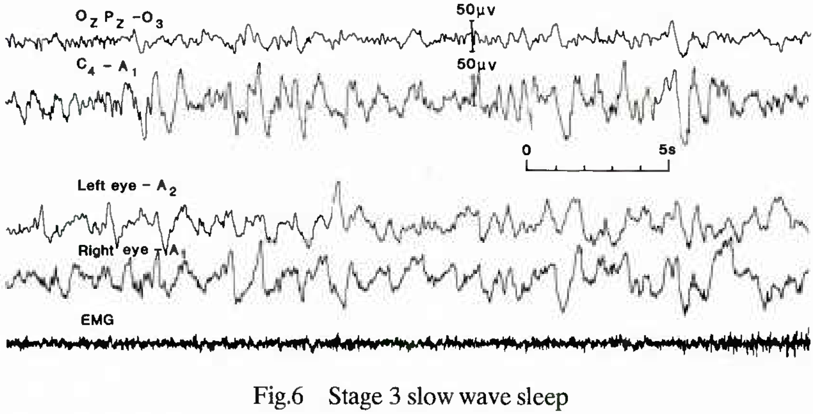

Fig.6 Stage 3 slow wave sleep

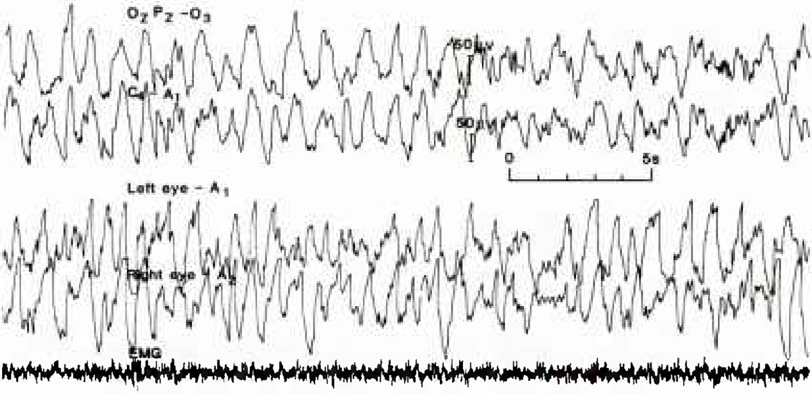

Fig.7 Stage 4 slow wave sleep

consists of waves of 2 Hz or slower with amplitudes greater than 75 µv from peak-to-peak the epoch is scored as stage 4 (Figure 7). Although only slightly more than half of an epoch may contain high amplitude slow waves, most stage 4 epochs have the appearance of being completely dominated by this activity. Intervals of lower amplitude, faster activity rarely persist for more than a few seconds in this stage, though they are more prominent in stage 3 sleep. Sleep spindles may or may not be present in stage 4.

Rapid eye movement (REM) sleep is indicated by the appearance of relatively low voltage, mixed frequency activity together with episodic eye movements (Figure 8). The electroencephalogram has some resemblance to drowsy sleep, but

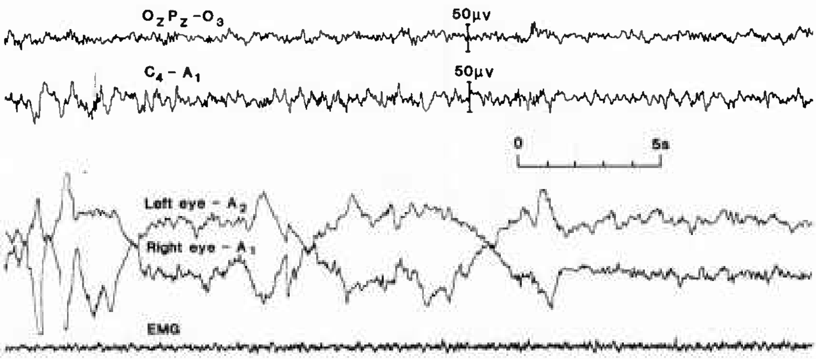

Fig.8 Rapid eye movement sleep with conjugate eye movements, and low amplitude myographic activity.

vertex sharp waves are absent. So-called "saw-tooth" waves appear frequently, but not always, in vertex and frontal regions in conjunction with bursts of rapid eye movement activity. Alpha activity may be more prominent than during drowsy sleep, although the frequency is generally 1 to 2 Hz slower than during wakefulness. There are no sleep spindles or K complexes. During rapid eye movement sleep the amplitude of the electromyogram almost always reaches its lowest levels, and is never higher than that of the preceding sleep stage.

SLEEP CYCLE

The healthy young adult passes quickly from waking into non-rapid eye movement (NREM) sleep (stages 1, 2, 3 and 4), and about 70-90 minutes elapses before the first period of REM activity. This interval is the latency to REM sleep. The normal sequence of sleep stages during the early part of the night is: waking, stage 1, stage 2, stage 3, stage 4, stage 3, and then stage 2. At this point the first period of rapid eye movement sleep occurs. It is followed by further non-REM stages (stages 2, 3, 4, 3 and 2), and then by a further REM episode. The interval from the beginning of one REM period to the beginning of the next is about 100 minutes, but it may vary between

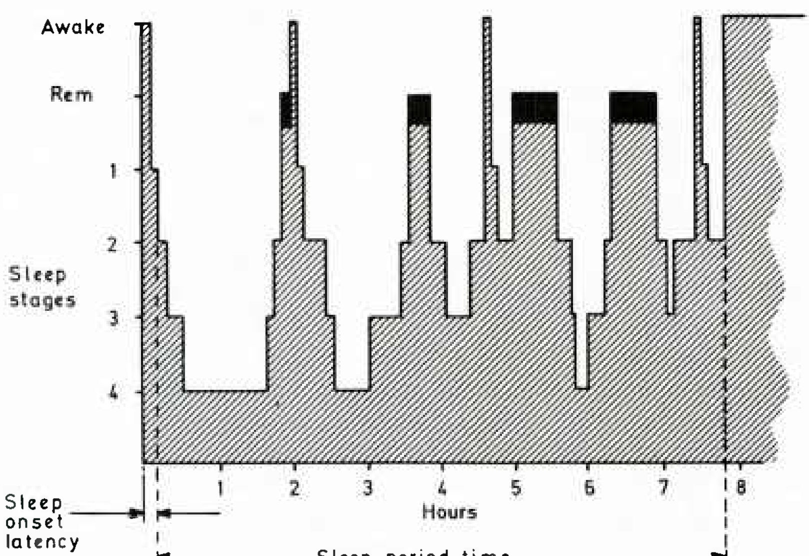

Fig.9 Nocturnal hypnogram in young adult.

70 and 120 minutes. As the night proceeds the content of the sleep cycle alters, and the later cycles of the night have less slow wave sleep. The REM episode of the first cycle is shorter than those in subsequent cycles. The night time sleep of a young adult is shown in the hypnogram (Figure 9). Typical percentages for the whole night in the young adult are: 50% stage 2, 25% stage REM, 10% stage 3, 10% stage 4 and 5% stage 1.

Some individuals who do not complain about their sleep or daytime function and whose sleep appears unbroken have substantially shorter or substantially longer than the average amount of sleep for their age. Short sleepers sleep less than three-quarters of the norm, and some may even sleep less than 3 hours each day. Long sleepers sleep at least 9 hours a day, possibly between 12 and 14 hours, and they enjoy and protect their sleep, and so may have difficulty in coping with restricted sleep schedules. There is no obvious psychopathology, though it has been suggested that specific personality traits may exist in the two groups.

DAYTIME SLEEP LATENCIES

The electroencephalogram may be used in the study of daytime alertness (multiple sleep latency test). Time taken to reach drowsy sleep is measured 5 or 6 times during the day (Figures 10 and 11). A low mean value over the day is found in individuals with disorders of sleep associated with excessive daytime sleepiness. However, many healthy individuals have low mean values, and so short latencies do not necessarily imply sleep pathology, but could indicate a relative ease of falling asleep.

SLEEP AND AGE

Total sleep time and the total nightly amounts of the various stages of sleep are related to age. Total sleep time is longest in infancy and it stabilises around 7 hours at about 20 years. It remains constant during adulthood and changes little throughout old age. The most obvious change with age is the decrease in slow wave sleep. In young adults about 20% is spent in slow wave sleep, but in late middle age few have stage 4, although more women than men show it in later years. Elderly men rarely show stage 4 sleep, but some is still present in women. Rapid eye movement sleep has the longest duration in infancy and in chidhood. There is a drop in the percentage of REM sleep from around 30% in young children to around 25% in adults, and there is another slight fall in the elderly.

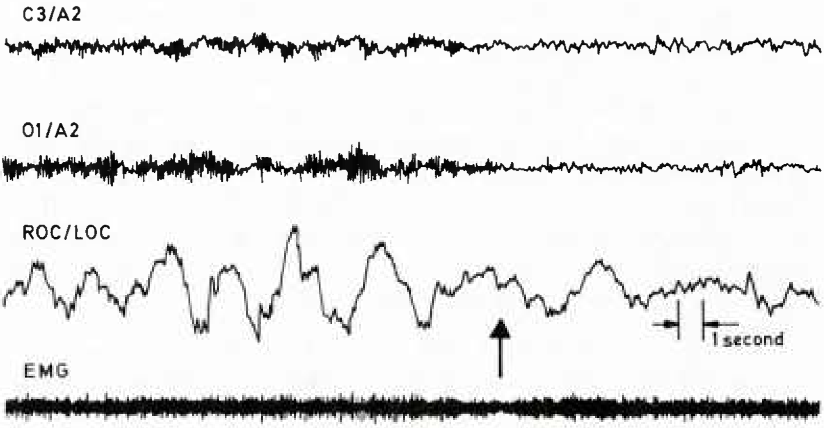

Fig.10 Onset of drowsy (stage 1) sleep during a daytime sleep latency test.

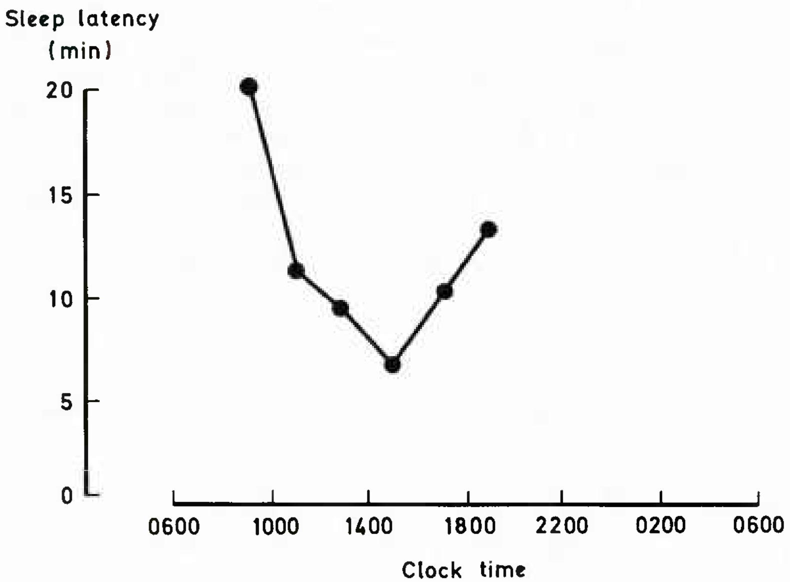

Fig.11 Daytime latencies to drowsy (stage 1) sleep for the multiple sleep latency test.

The number of awakenings increases with age, although the proportion of time spent awake during the night may change very little. Awake time in adults usually remains below 2% of the sleep period, though it tends to increase after 40 years in males and after 50 years in females. However, awake activity associated with arousals may be more than that suggested by the usual analysis of 30 second epochs. An awake episode of less than 30 seconds could be divided equally across two epochs, and so would not be scored as wakefulness in either epoch. This may be an important issue in the assessment of sleep in both middle age and in the aged.

Sleep becomes progressively disturbed in middle age. At this time of life many are coping with exacting lives. Their occupations are likely to involve irregularity of rest, and they may well have difficulty in achieving acceptable sleep. Sleep is less restful as we grow older and may be associated with spontaneous leg movements and changes in the usual pattern of breathing. Leg movements and apnoeas are often seen during the sleep of middle aged individuals who do not have any obvious complaint related to their sleep. Indeed, about two-thirds of middle aged males have leg movements (Figure 12), and around 90% have apnoeas or hypopnoeas (Figure 13). The incidence of these events appears to be spread evenly over the middle span of life, though some have an unusually high number. Both events may be associated with brief arousals and lightening of sleep, and leg movements which tend to occur during drowsy (stage 1) sleep are likely to be associated with disturbed sleep.

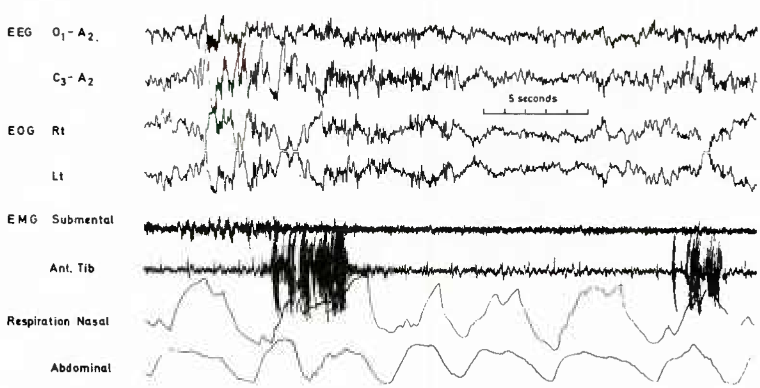

Fig.12 Leg movements during sleep may lead to an arousal.

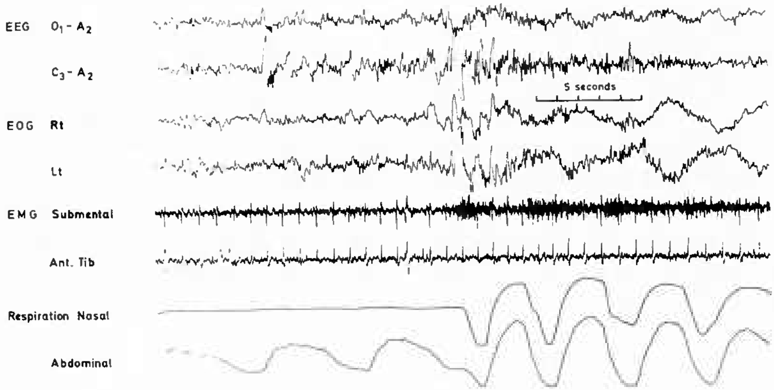

Fig.13 The end of an apnoea may be associated with an arousal.

AUTONOMIC ACTIVITY

During drowsy sleep the muscles start to relax, breathing becomes regular, body temperature begins to fall, but the subject can be aroused easily. After sleep onset sleep becomes progressively deeper, and it becomes more difficult to waken the sleeper. In stage 4 breathing is even, the heart rate, blood pressure and body temperature are all low. Rapid eye movement sleep, the stage in which most dreaming occurs, is associated with a general increase in

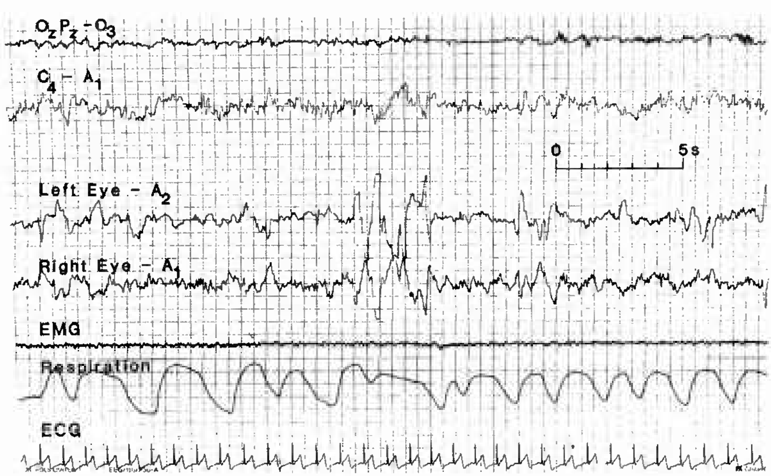

Fig.14 Irregularity of respiration during rapid eye movement sleep.

autonomic activity. Heart and respiration rates and blood pressure are increased, and REM onset is marked by an increase in the variability of these activities (Figure 14). There are more penile erections during REM sleep, the level of oxygen consumption increases and the oxygen supply decreases. There are also increases in the secretion and osmolality of the urine, an increase in cerebral blood flow, and a rise in brain temperature. However, some physiological measurements show decreased activity during REM sleep such as tonic chin muscle activity and muscle tone in the head and neck muscles.

NEUROENDOCRINOLOGY

The secretion of many hormones is related to sleep and wakefulness, to the sleep cycle itself or to specific electro-encephalographic activity. With some hormones the relationship also varies with age. Other influences include circadian rhythms (see Chapter 3), the light-dark cycle, and the episodic secretion of other hormones.

Growth hormone levels are usually very low during waking, except for secretory bursts associated with eating or exercise. In most subjects the peak plasma level of growth hormone is seen during the first 90 minutes of sleep and the secretion lasts from 1.5 to 3.5 hours. Smaller secretory bursts occur throughout the night, and these tend to be related to slow wave sleep as two-fifths of the bursts are observed during slow wave sleep which occupies only about 15-20% of total sleep time. Growth hormone secretion does not follow an independent circadian rhythm, and after inversion of the sleep-waking cycle the pattern of secretion is also reversed. The pattern of growth hormone secretion is not related to plasma levels of glucose, insulin or cortisol. Total 24-hour secretion of growth hormone remains similar even when the pattern and times of sleep are drastically altered, and, although the patterns of secretion differ greatly between individuals, the individual pattern is relatively constant.

The secretion of cortisol follows a well-defined circadian rhythm, with blood cortisol levels lowest in the early hours of sleep and highest in the early morning hours. Individual episodes of adrenocorticotrophic hormone (ACTH) secretion tend to occur about 10 minutes before an episode of cortisol secretion. ACTH secretion is lowest in the few hours before and after sleep onset, it increases after three to five hours of sleep and reaches its maximum just before awaking. Circadian rhythms of urinary 17-hydroxycorticosteroid persist during sleep deprivation, and lengthening or shortening of sleep time have no effect on the plasma cortisol cycle. The cortisol cycle adjusts to inversion of the 24-hour cycle within 1 — 2 weeks.

Since maximum plasma cortisol levels are normally reached after several hours of sleep, a relationship with REM sleep which is highest at that time has been suggested. Indeed, most peaks occur in or around REM episodes. Rapid eye movement sleep and cortisol secretion can, however, be dissociated, as in sleep inversion. In studies of temporal isolation, with desynchronisation of cortisol secretion from the sleep/wake cycle, inhibition of secretion occurs during the first hours of sleep irrespective of the circadian phase. This inhibition coincides exactly with the peak of growth hormone secretion.

The initial peak in prolactin secretion appears between an hour and an hour and a half after sleep onset, with subsequent peaks reaching maximum levels between 0700 and 0800 hours. During the hour after wakening the levels begin to fall, reaching a minimum between 1000 hours and noon. When the hours of sleep are modified, there is an immediate shift. In this sense prolactin secretion resembles that of growth hormone rather than ACTH, although it seems to have some stability as a circadian rhythm in addition to its relationship to sleep. However, unlike growth hormone, prolactin secretion does not seem to be related to a specific sleep stage.

The thyroid stimulating hormone (TSH) has a pronounced circadian pattern, peaking in the evening before sleep onset and falling during sleep. If sleep is delayed, thyroid-stimulating hormone levels climb for longer and this suggests that sleep initiates the fall in plasma level. However, sleep reversal studies have suggested that there is also an endogenous component. Thyroxine (T4) and triiodothyronine (T3) do not follow the same pattern as TSH. Sleep deprivation is associated with an increase in T3 and T4 levels, but TSH is not altered. Slow wave sleep is reduced in hypothyroidism, whereas hyperthyroid patients have excess amounts of this activity.

In adulthood, testosterone peaks during sleep and this pattern will follow any phase shift of sleep. The increase in testosterone occurs toward the end of sleep and this may be partly related to REM sleep. The effect of sleep is less for testosterone than for growth hormone or prolactin. There is, for example, a second secretory peak during waking. Testosterone and other gonadal hormones are markedly reduced by sleep deprivation.

It is well established that urine output decreases at night, during which about one-third of the 24 hour volume is excreted. Anti-diuretic hormone secretion, like that of the anterior pituitary hormones, is pulsatile, but there appears to be no relationship to sleep stages.

Melatonin is secreted principally by the pineal gland, although there is a secondary source in the retina. It is secreted at night and is suppressed by light of sufficient intensity. It has been suggested that melatonin given at an appropriate time preceding the sleep period would advance the circadian cycle, and in this way alter the endogenous oscillator. However, evidence is needed that melatonin has not merely distorted the observed rhythm, as this may be inadvertently interpreted as a phase shift, and to date published data are equivocal. There is no convincing evidence that melatonin shifts the basic oscillatory function in man, and the situation is further confused as the drug would appear to have psychotropic activity such as sedation and mood elevation, and may even encourage sleep by lowering body temperature. The activity of melatonin in man has not yet been adequately explored, and the claim that it may be used to shift circadian rhythms after a time zone change is premature.

CHAPTER 2

SLEEP DISORDERS

In the management of aircrew complaining of sleep difficulties it is useful for the aeromedical practitioner to be familiar with the varied causes of sleep disturbance in man. Sleep disorders or psychopathology should be included in the differential diagnosis, particularly in the middle aged if the primary complaint is that of persistent insomnia and/or excessive daytime sleepiness. The duration of the insomnia should first be considered. The chronic insomniac presents an unremitting history of disturbed sleep over months or even years, and careful assessment of the patient is essential. A history of a week or so (short term insomnia) is usually related to a life crisis or to a medical illness, and transient insomnia when sleep is disturbed over a day or two arises when the circumstances are not conducive to sleep or when rest occurs at unusual times.

The practitioner must always bear in mind that sleep disturbance in aircrew could be due to personal stress or various forms of illness, and that the persistent complaint of insomnia or, even more important, excessive daytime sleepiness may hide real pathology. Indeed, the persistent complaint of insomnia in aircrew should always be carefully investigated, and it is for this reason that we deal with disorders that lead to chronic insomnia or daytime sleepiness.

In many patients with a long history there is no obvious cause, and their condition is often referred to as primary chronic insomnia. Such individuals may complain of daytime sleepiness or simply loss of well-being, but on investigation show little evidence of sleep disturbance or of daytime sleepiness. They may have a neurotic attitude to sleep or may simply need more sleep than others. Some may have a major and chronic dissatisfaction with their lives, and express this dissatisfaction in physical terms.

Possibly one-third to one-half of patients with chronic insomnia have an underlying personality disorder or psychiatric problem, such as depression. Some may have been prescribed hypnotics several years ago for a specific reason, and continued their use without any real need. Others may abuse alcohol or even drugs. In some chronic insomniacs there are multiple arousals during the night due to somatic events such as apnoeas, leg movements and gastro-intestinal reflux. Sleep apnoeas and myoclonus are of particular interest as they are related, at least in part, to the normal deterioration of sleep in middle age, and they may be a relevant finding in aircrew having difficulty in coping with unusual patterns of work.

However, chronic difficulty with sleep may arise for reasons other than psychopathology or simply the usual deterioration with age. In one series of admissions to a sleep centre the sleep apnoea syndrome accounted for over one-half of patients who presented with the complaint of excessive daytime sleepiness. Nocturnal myoclonus and the restless legs syndrome are also associated with disturbed sleep, and it must be remembered that narcolepsy does not only present itself in young adults. Indeed, in the same series narcolepsy accounted for 30% of the patients. Sleep related conditions can prejudice the ability to remain alert during the day, and it is for this reason that we look in some detail at three of the commonest sleep syndromes and the parasomnias.

NARCOLEPSY

Excessive daytime somnolence always merits careful investigation. Narcolepsy is a prevalent cause, and though it is most frequently encountered between 15 and 25 years, the age of onset varies from childhood to the early fifties. The incidence is between 1 and 2 per 1,000, and it is more frequently seen than many more familiar neurological diseases such as multiple sclerosis. The patient suffers from excessive daytime somnolence, and in addition may show one or more of three other well established features — cataplexy, sleep paralysis and hypnagogic hallucinations. There may also be disturbed nocturnal sleep with awakenings, body movements and little slow wave sleep, and excessive rapid eye movement sleep. The features related to wakefulness are more frequent, but probably only 1 in 10 patients suffers from the complete tetrad. Aetiology is unclear. A chronobiological basis is now considered unlikely, but genetic influences are important and there are associations with the HLA-DR2 antigen.

The primary and most disabling symptom is drowsiness which leads to short periods of daytime sleep, sometimes prevented by concentrating on staying awake. They occur at inappropriate times and last for 10 — 15 minutes, though if resting patients may fall asleep for a couple of hours. These naps are usually, but not necessarily, refreshing. The attacks may occur with or without warning, and are common in situations which provoke drowsiness such as after lunch and during afternoon lectures, though they are not always related to monotonous activity. Patients not only feel sleepy, but also spend their days at a low level of alertness which may lead to poor work and memory lapses. A positive diagnosis requires a minimum of one of the major factors — either irresistable episodes of sleep or attacks of cataplexy — together with REM episodes immediately or within ten minutes of sleep onset (Figure 15). Daytime sleep recordings are useful to establish whether sleep onset REMs are present.

The most common symptom related to wakefulness is cataplexy. It occurs in some form or another in at least two-thirds of patients. When fully conscious patients suffer from a sudden decrease or abrupt loss of muscle tone which may be generalised or limited to certain muscle groups. There may be a transient weakness of the jaw or in extreme cases postural collapse. An attack may last for only a few seconds, and is frequently triggered by exercise or emotion, such as laughing, crying, anger, excitement and joy. The latter part of the attack may pass into rapid eye movement sleep. It may occur many times a day, or once a week or even less, and may disappear completely.

Sleep paralysis and hypnagogic hallucinations occur while falling asleep or on waking, and recordings reveal REM sleep during these events. In sleep paralysis the patient feels he cannot move any muscles except those controlling the eyes, and this state is often accompanied by intense fear and by hypnagogic hallucinations. Respiration is not affected, and the paralysis can be terminated by

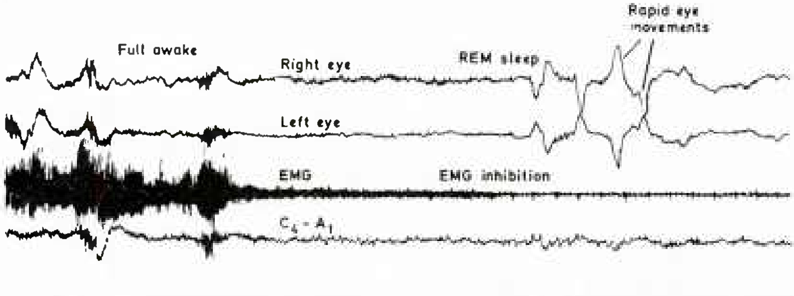

Fig.15 Recording during sleep onset in a narcoleptic subject with the immediate appearance of rapid eye movement sleep. *Reproduced from Hauri, P. (1977), The Sleep Disorders. By kind permission of the Upjohn Company.*

vigorously moving the eyes or by being touched. It lasts from a few seconds to several minutes. Hypnagogic hallucinations are vivid, frightening auditory or visual hallucinations experienced when fully conscious, and they often occur during an episode of sleep paralysis. Sleep paralysis and hypnagogic hallucinations are each present in about a quarter of patients with narcolepsy.

There is no consistent psychopathology associated with narcolepsy, though the patient may be considered as lacking motivation and having little interest in work. Often the background will include episodes of a disciplinary nature, and in about half there is a history of abrupt changes in the sleep-wakefulness cycle, or recent personal distress. Narcolepsy can lead to driving accidents, a disrupted social life and depression. Treatment is somewhat uncertain though excessive daytime sleepiness may be alleviated by stimulants, and if cataplexy is serious, some drugs used as antidepressants (such as clomipramine) may be helpful.

Idiopathic and recurring hypersomnia need to be distinguished from narcolepsy. In idiopathic hypersomnia, hypnagogic hallucinations, cataplexy and sleep paralysis are absent, sleep episodes are of longer duration and less irresistable without being refreshing, and there are no sleep onset REMs. Recurring hypersomnia is a manifestation of the Klein-Levine Syndrome, and involves episodes of excessive somnolence, over eating and abnormal behaviour, and may also be a feature of depression.

SLEEP APNOEA SYNDROME

The sleep apnoea syndrome most commonly affects overweight males, especially between the ages of 40 and 60 years. There is excessive daytime sleepiness, and frequent apnoeas during sleep. The syndrome can usually be recognised because of the history of loud intermittent snoring while recordings reveal apnoeic episodes in both REM and non-REM sleep. There may be an absence of respiratory effort with cessation of diaphragmatic movement with the upper airway open even though there is no airflow (central apnoea), or there may be airways obstruction with excessive respiratory effort (obstructive apnoea).

Because of the disturbed nocturnal sleep and hypoxaemia patients complain of excessive daytime sleepiness, and may take frequent though unrefreshing naps during the day — often at inappropriate times. The football fan may fall asleep at the match,

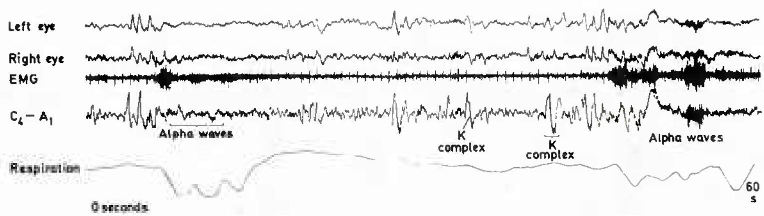

Fig.16 Sleep apnoea. As the patient falls asleep breathing is arrested, and when breathing starts again there is an arousal. *Reproduced from Hauri, P. (1977), The Sleep Disorders*

and the teacher may fall asleep in front of the class. Obesity, in particular, and possibly depression may be associated with the condition. Nearly all are heavy snorers, and the diagnosis must always be considered in a patient who snores and complains either of excessive daytime sleepiness or insomnia.

The sleep apnoea syndrome evolves gradually from heavy snoring with apnoeas and daytime somnolence to the complicated form with cyanosis, polycythaemia, right heart failure and oedema, enlargement of the liver, papilloedema and coma. Investigation should include studies of respiratory function during sleep as well as conventional sleep recordings (Figure 16). There may be mechanical abnormalities of the soft palate and jaw, laryngeal stenosis or even neurological disorders or some functional impairment such as decrease in the tone of the oropharyngeal musculature during sleep. In cases with either severe complications or excessive daytime sleepiness which compromises their work a tracheostomy which is opened during sleep may be necessary. Alternative surgical measures may be appropriate such as uvulopalatopharyngoplasty, though all do not benefit to the same degree. Weight reduction and sleeping on the side may help, and positive pressure breathing at night is advocated by some specialists. Protriptyline, 20 mg daily, may lead to improvement possibly due to an effect on upper airway muscular tone.

RESTLESS LEGS SYNDROME

Rapid, sporadic muscular movements often occur during sleep, particularly during REM sleep, and sometimes there are massive jerks which may involve a limb or even the whole body. These are of little clinical importance, but frequent leg movements may lead to

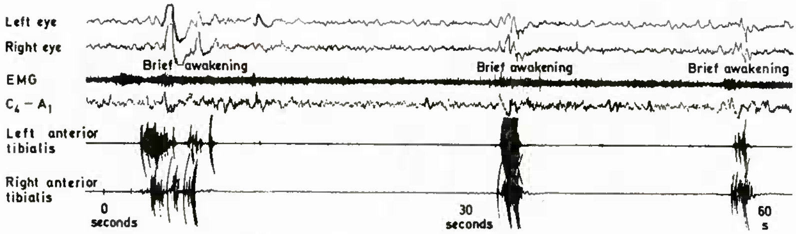

Fig.17 Nocturnal myoclonus. There are periodic twitches every 20 to 40 seconds in the tibialis muscles, and each is accompanied by an arousal. *Reproduced from Hauri, P. (1977), The Sleep Disorders.*

sleep disturbance. In nocturnal myoclonus leg twitches repeat themselves every 20 — 40 seconds during sleep (Figure 17), and recordings from muscles such as the anterior tibialis show bursts of activity, with the episodes lasting from 5 minutes to 2 hours, and alternating with normal periods of sleep. In some individuals there are complaints of insomnia. The restless legs syndrome is characterised by similar jerks, but there are uncomfortable and disagreeable sensations of cramp deep inside the calf muscles when at rest or in bed about to fall asleep. The sensations may be ameliorated by rubbing or movement of the legs. This condition can cause severe insomnia, though alterations in the sleep electroencephalogram are limited to arousals. Benzodiazepines may improve sleep continuity, but do not diminish myoclonic activity.

PARASOMNIAS

The parasomnias are paroxysmal disorders arising within sleep, and are mainly encountered in children. Most occur during a particular stage of sleep, and this often determines the nature of the condition. The disorders may be related to sleep onset, slow wave or rapid eye movement sleep, though some may appear in all stages of sleep.

Dream like hallucinations at the time of falling asleep are often experienced by normal individuals, but sometimes they become threatening and may lead to fear of sleep and sleep onset insomnia. Sleep talking and tooth grinding occur during the light stages of sleep. Sleep talking is a benign condition, but tooth grinding can lead to dental and mandibular pathology. Enuresis can occur at any time of the night, and is more common in males. Enuretics are usually deep sleepers. Treatment in the adult must exclude any organic cause as idiopathic enuresis is rare.

Nocturnal sleep drunkenness, sleep walking and sleep terrors occur during an arousal from slow wave sleep, and therefore tend to appear in the first part of the night. In sleep drunkenness the sleeper awakens with marked confusion and, rarely, with aggressive behaviour. In sleep terrors the individual sits up in bed and screams, and may sleep walk. Adults with sleep terrors have a high incidence of psychopathology with depression and phobia. In sleep walking the individual gets out of bed and walks some distance without stumbling or falling over the furniture, but most outgrow this condition.

Anxiety dreams and aggressive behaviour may be linked to REM sleep and occur during the latter part of the night. Adult sufferers from anxiety dreams have a high incidence of mental disease with schizoid personality and sometimes schizophrenia. Sometimes arousals from REM sleep can be associated with aggressive behaviour, and there may be a neurological basis for the disorder.

CHAPTER 3

CIRCADIAN RHYTHMS

Biological processes may vary with respect to time in a periodic and regular manner, and such rhythms are present throughout nature from nucleated unicellular organisms to man. In man they involve the entire organism, as well as systems, organs and tissues, and they influence both his physiological and psychological activity. They persist in the absence of time clues and cues, though they are modulated by variations in the environment. The period (time to complete a cycle) of these rhythms is often synchronised to some major environmental cycle, such as the tidal (12.4 hours) rhythm of shore dwelling species and the annual rhythm of reproductive function of many mammals and birds. In man, as in many other species, the commonly observed rhythm is that which oscillates once around the length of the solar day (24 hours), and such rhythms are termed circadian.

The point during the period at which the maximum value is expected to occur is known as the acrophase. For example, it could be the time of day when body temperature is highest. Since the acrophase is located on a time-scale, a phase reference is usually given, and this is usually midnight for a circadian rhythm. The magnitude of the variation of the rhythm is known as the amplitude. Range of the oscillation may be used when a rhythm is not symmetrical.

ORIGIN OF RHYTHMS

Daily rhythms of sleep and wakefulness, urine production and body temperature are well recognised, but the question arises whether they originate from within the organism or are the result of some exogenous influence. Alternation of sleep and wakefulness and/or physical activity have a direct effect on temperature and other rhythms, and this is known as the masking effect. Activity raises deep body temperature and sleep or rest lead to a reduction in body temperature, independent of and superimposed on the circadian increase and decrease in this variable. However, temperature continues to rise and fall in the absence of external influences, and has therefore an endogenous rhythm.

Circadian rhythms are free running, self-sustaining oscillations with a periodicity between 23 and 26 hours. They are modulated by environmental synchronisers with an exact 24 h period related to the rotation of the earth. Synchronizers, which are also known as cues, entraining agents or zeitgebers, include light and temperature and their often dependent functions such as work schedules and sleep periods. Endogenous circadian rhythms have been established for many physiological, biochemical and psychological variables, and their times of maxima and minima, as well as amplitude, differ.

However, circadian rhythms may be influenced by variations in the environment, and in any particular situation there may be single or multiple cues. The majority of circadian rhythms are considered to be due, at least in part, to the possession of an endogenous oscillator. The possession of such an oscillator is thought to allow an organism to fit better into its rhythmic environment; for example, to prepare while asleep for the stresses of the next day. In addition to temperature, excretory and activity rhythms, there are circadian rhythms of the electrical activity of the brain, cell division, and serum content of specific substances, examples which are given in Figure 18. Circadian rhythms of temperature, 17-OHCS, adrenaline and noradrenaline are illustrated in Figure 19.

By the first week of life some rhythmic activity is apparent, though the rhythms of premature babies develop later than those of full term infants. Skin resistance peaks in the late morning and there is a sleep-wakefulness pattern with a period around 24.4 hours. Infants exposed to a 4 hourly regular routine tend to develop the sleep-wakefulness rhythm sooner than those reared alone or fed on demand. It has been proposed that organs which are well developed at birth such as the skin show a circadian rhythmicity earlier than those which take longest to mature. In this way functions within the same organ may develop rhythmicity at different times. Water excretion which depends principally on glomerular filtration shows a circadian rhythm before electrolyte excretion which is dependent on tubular function.

PERFORMANCE

On most, if not all, tasks performance rises during the day to a peak or plateau between 1200 and 2100 hours, and falls to a minimum usually between 0300 and 0600 hours. The pattern is similar to that of body temperature, and has been shown for a large

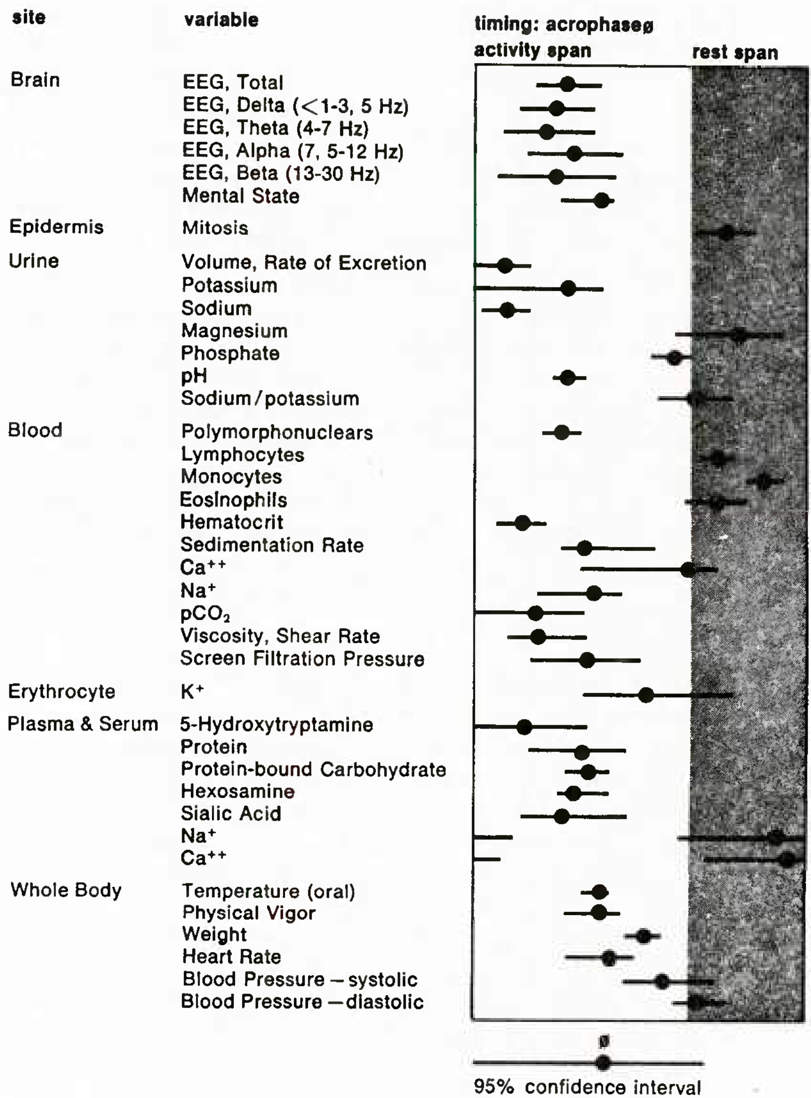

Fig.18 Circadian acrophases for various physiological functions in man. *Reproduced from Reinberg, A. (1974), Fourth Dimension of Medicine. By kind permission of the Upjohn Company.*

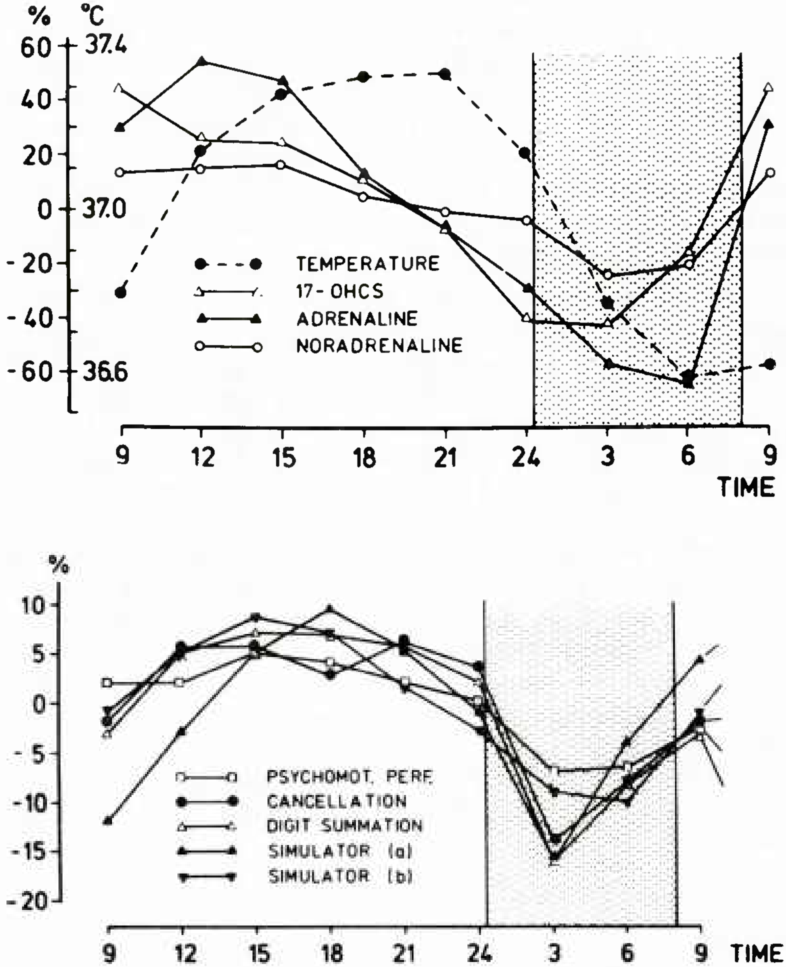

Fig.19 Circadian rhythms of some physiological and psychological functions in man. *Reproduced from Klein, K.E. & Wegmann, H.M. (1980) AGARDograph No 247.*

number of skills including addition, cancelling symbols, vigilance, card sorting and choice reaction, as well as performance on an aircraft (F104) simulator. Some of these patterns are illustrated in Figure 19. There is some doubt whether the correlation between performance and temperature changes is the same for tasks involving short term memory, though the suggestion that memory skills peak in the morning and fall steadily during the day has not been confirmed. A task with a high memory load tends to adapt faster than other tests to simulated night work, and to the time shifts inherent in transmeridian flight.

Many factors may modify performance rhythms. If subjects stay awake the phase of the rhythm tends to drift toward later hours, and during the first night awake the range of oscillation is smaller. As sleep deprivation continues the range of oscillation may increase again, though the 24 hour mean of performance will fall. The effects of sleep deprivation are augmented by uncertainty in the task and in the response required. There have also been attempts to link behaviour and personality with rhythmicity in performance (Figure 20). Those who perform well in the evening tend to have later maxima and minima of performance than those who perform well in the morning, and their spontaneous period in the free running state is longer. However, correlations with extroversion and introversion scores, though described, are not strong. Further, practice and extra effort will reduce the amplitude of performance rhythms, while workload and the stress imposed by the task, will increase amplitude. The range of oscillation tends to be low for simple tasks with highly motivated subjects, and high for complex tasks with subjects with poor motivation.

Performance over long periods of time may also be influenced by an interaction with the circadian system. Performance degradation may depend on the stage of the circadian cycle with which it coincides. With prolonged duty, the maximum performance decrement can range from between 10 and 15%, to as much as 35% when the end of the prolonged duty coincides with the dip in the circadian rhythm. It would appear that the increasing levels of arousal during the day partly compensate for the effect of prolonged work whereas the natural decrease in alertness at night may add to the problem. Auditory vigilance as well as tests related to instrument flying in simulated transport flights show this pattern. The inclusion of a sleep period during long periods of work is of benefit. When work periods of four hours duration starting at 2000 h and 0400 h

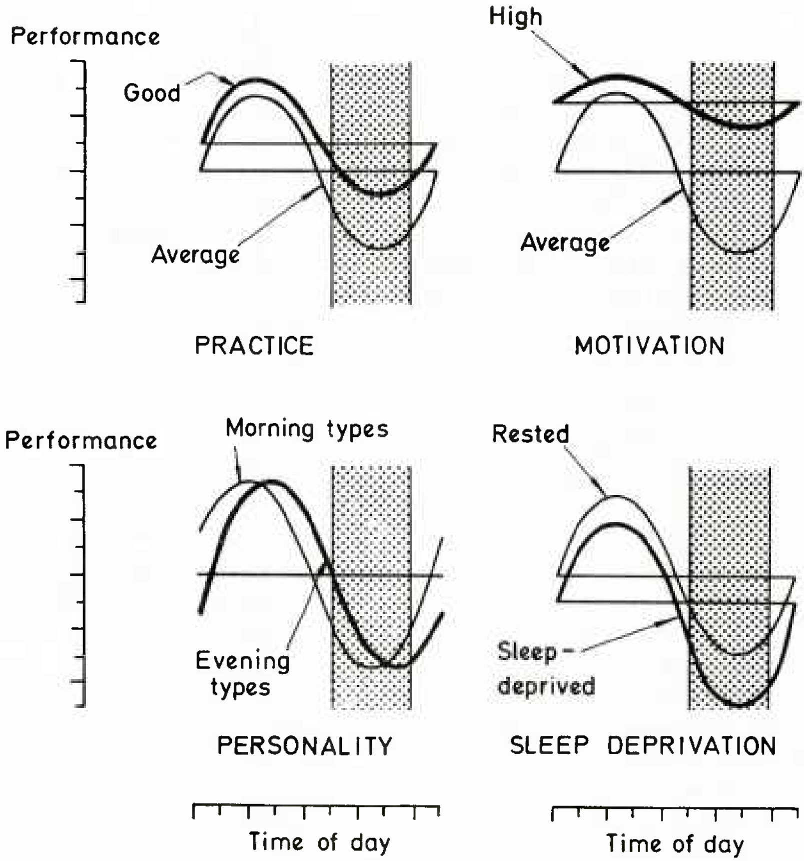

Fig.20 Schematic representation of the factors which may modify circadian behavioural rhythms. *Adapted from Klein, K.E. et al. Aviation Space and Environmental Medicine (1976) 47, 221-230.*

are separated by a period of sleep, the fall in performance at the circadian trough is reduced.

PHYSICAL ACTIVITY

Physical activity may also modify performance and its circadian pattern. Light to moderate exercise improves mental performance whereas heavy work decreases performance, and the effect is dependent on time of day as well as the task being studied. Studies on visuo-motor coordination have shown improvements in the morning and afternoon after a period of exercise, but this is not so in the late evening and early night. On the other hand the same exercise tends to impair tests of memory at any time of the day. Heart rate at rest also shows a circadian variation of about 8 — 12% with the minima occurring at night, though the difference decreases with increasing physical workload and is near zero at maximum effort. The usual prediction of aerobic work capacity from heart rate at submaximal exercise does not therefore hold when the circadian rhythmicity of physical performance is considered. At night the oxygen consumption in relation to work output is lower at maximum effort, and work outputs equivalent to those during the day can only be produced with a higher physiological cost with about 8 — 10% extra oxygen uptake.

CIRCADIAN RHYTHM DISTURBANCE

Human beings experience a regular alternation of sleep and wakefulness which is in synchrony with the rotation of the earth. The most important environmental influence on the phase of circadian rhythms is almost certainly the daily alternation of light and darkness, and in the absence of the periodic time cues of the environment, as when living in caves, the rhythm is no longer entrained and is free-running. It then has a period of about 25 hours, and this is the intrinsic rhythmicity of man — an internal 'biological clock' which keeps time in the absence of environmental cues. It is important to realise that many other factors can influence circadian rhythmicity, and that the rhythm may be easily modified by external events. Examples include the suppression of melatonin by bright light, the effect of posture on aldosterone secretion and the effects of sleep and exercise on body temperature. Such effects are transient modulations of the rhythm, and do not imply a fundamental change in the clock mechanism.

In man, as well as the light-dark cycle of the environment, the clock hour and day time-related social activities, such as meals, work and rest — in particular the beginning and end of sleep — are also important in entraining rhythms. It is the inability to adapt to a sudden shift of these external synchronisers which causes a transitory desynchronisation of the circadian rhythmicity of the individual with that of the environment. Such a dissociation of circadian rhythms may be brought about in many ways. Abnormal time routines may be imposed, isolation from time cues may be effected, and rapid phase shifting across a number of time zones follows transmeridian flights.

Subjects can be almost perfectly isolated from natural time cues in deep caves, underground bunkers and isolation chambers. Under such constant conditions the circadian system will free run, and most subjects will show a spontaneous period close to 25 hours. In the free running situation most rhythms remain synchronised with each other, but in some individuals the period length of activity rhythms may vary from 30 to 40 hours whereas the temperature rhythm maintains a period around 25 hours. Rapid eye movement sleep, plasma cortisol release, urinary potassium excretion, sleepiness, and some aspects of performance are linked with body temperature, while slow wave sleep, growth hormone release, urinary calcium excretion and skin temperature are linked with rest and activity. This is called internal desynchronisation and has been taken to indicate the presence of two internal oscillators. However, sleep duration is dependent on body temperature and, therefore, the two rhythms are still linked in some way. Free running circadian rhythms seen under constant conditions can be modified by external stimuli, which act as artificial synchronisers. However, there is a limit to the period length which can be superimposed.

In the world outside conflict of the circadian rhythm with that of the environment can also arise. The zeitgebers in the environment may change their period length, become weakened or disappear completely. This occurs in submarine and space operations, but, in principle, is also present in other situations of partial or total removal from external periodic inputs, such as living in the Arctic, or in the confinement of a shelter. When rest and activity patterns are out of phase with the environmental synchronisers, conflict may also arise, and this condition is found in shiftworkers particularly when night work is undertaken. Finally after transmeridian flight there is a phase shift in the environmental timing system, and this change may be repeated often in aircrew involved in world-wide operations. The ability to sleep varies with the phase of the temperature cycle, and it is because the oscillator is slow to change that it is difficult to adjust sleep rapidly after a time zone change or after a shift in the work-rest cycle.

Circadian rhythmicity may also be disturbed in disease. The rhythmic activity of the electroencephalogram and that of plasma 17-OHCS may be desynchronised in epilepsy, circadian oscillations of several functions may be increased in diabetes and the amplitude of many rhythms may be decreased in psychoses. The peak time for attacks of asthma and myocardial insufficiency is around 0400 h. Sensitivity to some drugs also varies with time of day. Cardiac patients are more sensitive to diuretics in the evening than in the morning, and to digitalis at night than during the day. The response of diabetics to insulin is maximum around 0400 h, and the maximum rate of alcohol metabolism occurs between 1400 h and midnight.

SLEEP DISORDERS

There are disorders of sleep which arise from modulations of circadian rhythmicity. In the delayed and advanced sleep phase syndromes sleep onset and wake time are later or earlier than desirable, but sleep occurs at the same clock time each day, and there is no difficulty in maintaining sleep once it has begun. The delayed sleep phase syndrome is usually seen in young people, and often presents with the complaint of difficulty in falling asleep at the conventional time. There may also be problems with getting up in the morning, and if sleep is curtailed there may be daytime sleepiness. The advanced sleep phase syndrome is much less common, and does not interfere with daytime alertness. The complaint is that of an inability to stay awake in the evening, and to maintain sleep until the morning.

Some other disorders may also be interpreted as modulations of circadian rhythmicity. The inherent circadian sleep-wakefulness period is usually around 25 h, and so sleep and wakefulness may occur at a later clock time on successive days if entrainment to the cycle of the rotation of the earth is weak. Further, complete loss of the entrained rhythm could lead to an irregular sleep-wakefulness pattern with frequent daytime naps and excessive bed rest. Sleep at night is not adequate even though the total amount of sleep may be within normal limits.

CHAPTER 4

HYPNOTICS

Increasing understanding of the nature of insomnia has led to the more appropriate use of hypnotics in the management of sleep disturbance. There has never been any doubt that hypnotics reduce wakefulness, but there has been less certainty concerning their place in the management of disturbed sleep. It is now generally accepted that the initial approach to chronic insomnia must be that of assessment, and that the most appropriate use of hypnotics is in those with unequivocal evidence of disturbed sleep. It is in the latter context that the aeromedical practitioner must be familiar with the clinical pharmacology of hypnotics.

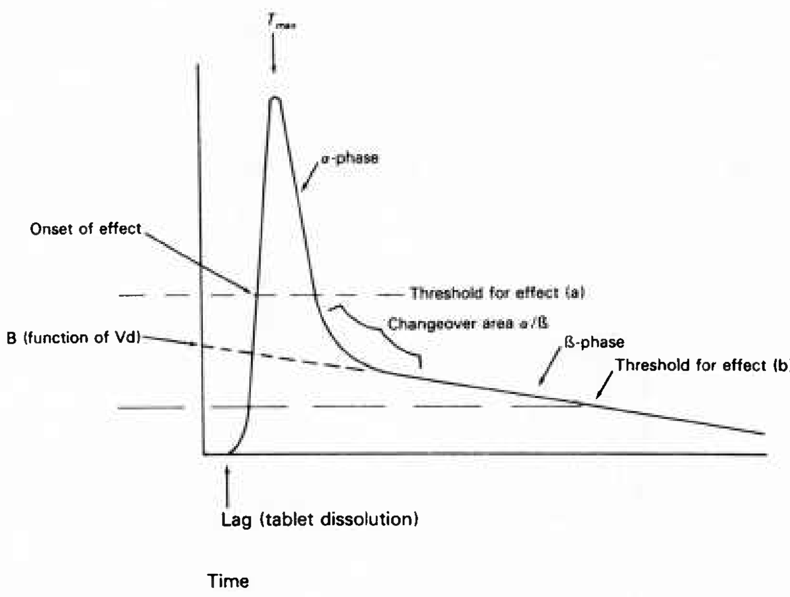

Fig.21 Plasma concentration profile (Semi-log plot) for a drug with a biexponential decay after oral dosing. There is an effect as long as the concentration remains above a certain level. The threshold may be related to the distribution or elimination phases. If it is above the concentration at which the inflexion of the distribution and elimination half lives occurs then it will be related to the distribution phase, and any effect will be of short duration.

PHARMACOKINETICS

In the practice of aviation medicine the most important property of hypnotics is their persistence of action, and this depends on absorption, distribution and elimination (Figure 21). The rate of absorption determines onset of action since hypnotics penetrate the blood-brain barrier easily. Adequate absorption is associated with a quick onset of action, whereas with slow absorption the desired effect may be attenuated or even absent. An adequate rate, ie peak plasma levels around an hour after ingestion, is necessary if a drug is to be used as an hypnotic, whereas slow absorption is more appropriate for the treatment of anxiety where a sustained effect with minimal initial drowsiness is sought (Figure 22). After absorption an hypnotic is distributed to the blood and to highly vascular tissues such as the brain, heart, lung and liver, and peripherally to tissues of lesser vascularity such as voluntary muscle. The initial fall in the plasma concentration may be quite marked and this relates primarily to the distribution of the drug, whereas the latter part of the fall relates to elimination by metabolism and by excretion.

However, it must be appreciated that the half life of a drug, though a familiar concept, has limitations in defining the

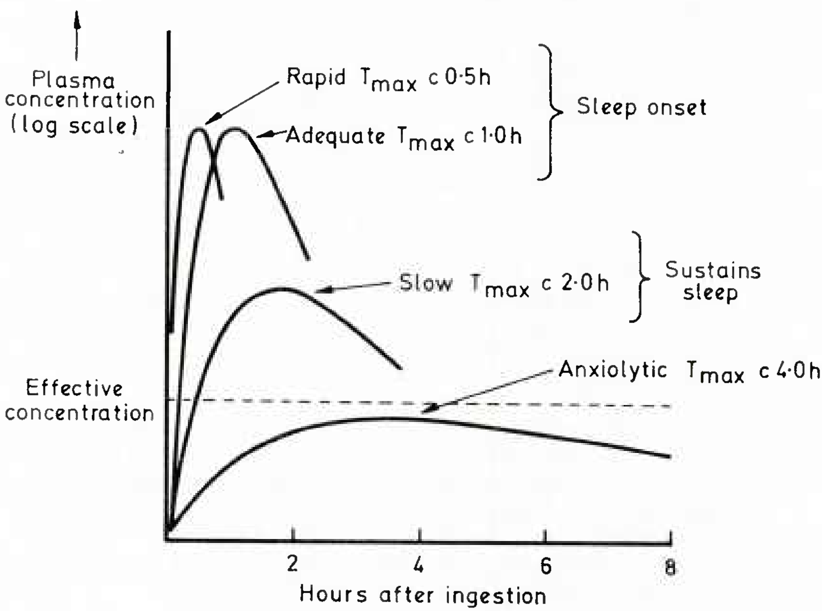

Fig.22 Relations between absorption, and onset and duration of action.

pharmacokinetic profile of an hypnotic. The elimination half life is directly dependent on the volume of distribution of the drug and inversely on its clearance, and duration of activity after single doses is more related to distributed than to elimination. With repeated ingestion the elimination half life becomes a more useful concept as it predicts the rate and extent of accumulation.

In general, as hypnotics cross the blood-brain barrier with ease, a drug has a particular pharmacodynamic effect as long as its plasma concentration remains above a certain level. If this level is within the phase which predominantly represents distribution, then the duration of action will be short, but if the level is within the elimination phase, which may be much slower than the distribution phase, it may be much longer. Distribution as well as elimination influence duration of activity, and so a relatively short duration of action may be attained with a single dose of a drug which is not rapidly eliminated. The influence of distribution on plasma concentration is important, and it follows that using the elimination half-life alone to indicate duration of action can be misleading (Figure 23). The elimination half-life may provide a relative estimate

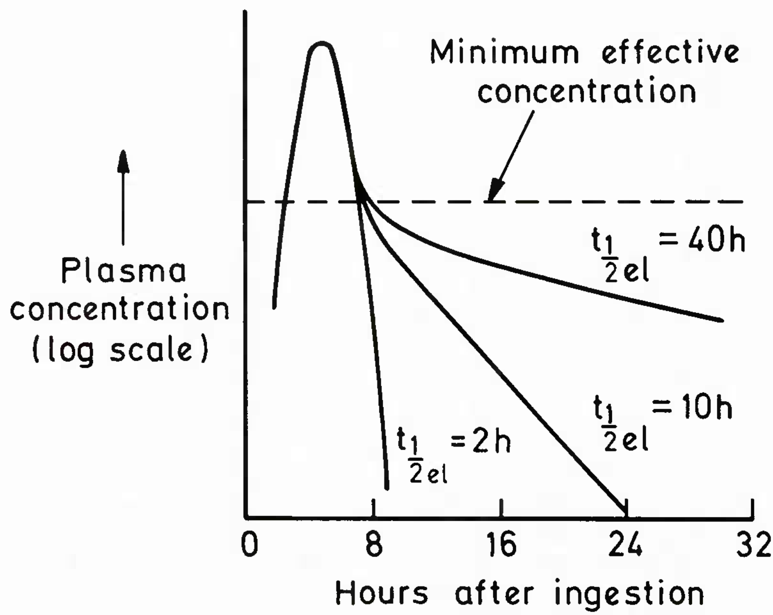

Fig.23 The duration of activity after a single dose may be similar in drugs with different elimination half lives.

of duration of action when the drugs in question have comparable absorption and distribution, or, as with some rapidly eliminated drugs, when elimination is by far the most dominant feature of the plasma decay, assuming again that they are absorbed in a similar manner.

The various hypnotics which are available may be considered in two broad categories. Some have a pharmacokinetic profile in which the separate parts played by distribution and elimination in the decline in plasma concentration are clear, and some have an essentially monoexponential decay. The duration of action of drugs which have a clear biexponential profile depends on distribution and elimination, and with some of these drugs it is relatively short because the initial decay is primarily due to a marked distribution phase. Nevertheless, continued nightly ingestion may still lead to accumulation if elimination is relatively slow (Figure 24), and the effect of repeated ingestion can be complicated further by accumulation of a slowly eliminated metabolite. It is for these reasons that a persistent effect may only be avoided in drugs with marked distribution but relatively slow elimination when they are used occasionally.

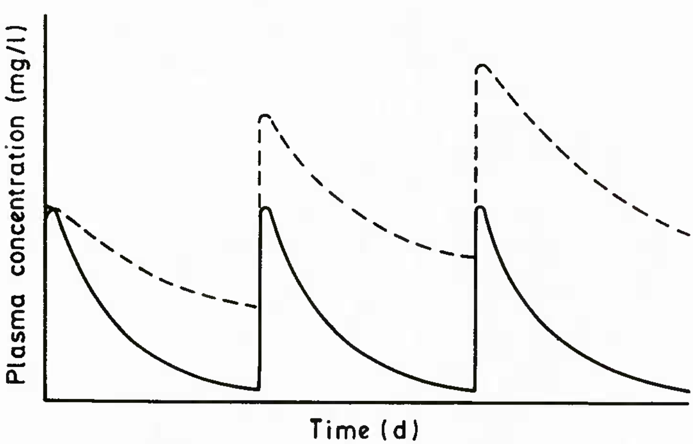

Fig.24 Plasma concentration profiles of two hypnotics with different elimination half lives (lower curves — 6 h; upper curves — 24 h) given every 24 h. If the compound with the half life of 6 h is given daily there will be no accumulation, and there will be an intermittent type of drug action. However, the drug with an elimination half life of 24 h will accumulate with daily ingestion.

Clearly, slow elimination of parent compounds or of metabolites is disadvantageous if drugs are to be used on a nightly basis, and freedom from daytime effects is sought. However, a minor alteration in chemical structure may avoid this problem. For example, temazepam has a distribution phase similar to that of its parent compound, diazepam, but does not accumulate on daily ingestion and does not have a slowly eliminated metabolite. Thus, daytime effects are highly unlikely unless inappropriately high doses are used. Diazepam and temazepam illustrate the parts played by distribution and elimination of parent compounds and their metabolites, and show that several factors must be borne in mind when the activity of any drug with a biexponential decay is under consideration.

Currently available hypnotics with an essentially monoexponential decay profile provide a wide spectrum of elimination rates, and so a variety of durations of action. The distribution phase does not play a significant part in the fall in plasma concentration for those drugs which are slowly eliminated, but it may contribute to the fall in plasma concentration for those which are rapidly eliminated, though in each the rate of elimination provides a good indication of the duration of action.

Drugs which for all clinical purposes have a monoexponential profile can be divided conveniently into two groups. Some are slowly eliminated and accumulation occurs on continued nightly ingestion, and some are rapidly (elimination half life around 5 hours) or even ultra-rapidly (elimination half life between 2 — 3 hours) eliminated. The slowly eliminated group includes flurazepam and chlorazepate with their metabolites, desalkylflurazepam and desmethyldiazepam, respectively, and ingestion will lead to a persistent effect. This may be useful clinically as with chlorazepate in the treatment of insomnia with an anxiety component. Tolerance, at least subjectively, may develop to drugs which accumulate, and unwanted drowsiness may only be experienced early on in the course of therapy, but such subjective impressions do not necessarily imply absence of daytime effects.

In the practice of aviation medicine, there is much interest in the rapidly and ultra-rapidly eliminated drugs, and several are available or are likely to become available in the near future. Midazolam, triazolam and zolpidem are ultra-rapidly eliminated with half-lives of around 2 to 3 hours, while brotizolam and zopiclone are more usefully described as rapidly eliminated, and have mean elimination half-lives of around 5 hours. Both ultrarapidly and rapidly eliminated hypnotics in appropriate doses are free of residual effects the next day and of accumulation on continued nightly ingestion, but the rapidly eliminated drugs have the greater potential to sustain sleep. Compounds like brotizolam and zopiclone are not only more likely to sustain sleep than ultra-rapidly eliminated drugs but are also more likely to sustain sleep than drugs whose pharmacokinetics involve a marked distribution phase.

CLINICAL CONSIDERATIONS

An hypnotic may be used to shorten sleep onset when there is difficulty in falling asleep, to reduce nocturnal wakefulness, or to provide an anxiolytic effect during the next day when insomnia is accompanied by anxiety. The purpose of an hypnotic is to alleviate one or more of these clinical problems, though a useful compound may meet only one criterion. It is unclear what improvement in sleep is required to constitute efficacy. However, the lowest dose which provides evidence of a beneficial effect on sleep in an appropriate group of healthy subjects is likely to be the lower dose of the recommended range. With this approach, the use of unnecessarily high doses in some, if not many, will be avoided.

In general, hypnotics are adequately absorbed and so most are useful for difficulties in sleep onset. Some hypnotics are absorbed very rapidly, and an example is midazolam in which peak plasma concentrations may be reached in less than half an hour after ingestion. The advantage of very rapid absorption is that a very low dose may be quite adequate for improving difficulties with sleep onset. However, some hypnotics are slowly absorbed (oxazepam and particularly loprazolam), and some are available in alternative formulations which have different rates of absorption. An example is temazepam with a soft gelatine capsule formulation (Normison-Wyeth) which is adequately absorbed with a mean delay to peak plasma concentrations of less than 1 hour. This formulation in the dose range 10 to 20 mg is useful for difficulties with sleep onset, but other formulations may be more slowly absorbed, and a higher dose may then be used in an attempt to produce an immediate effect, but this may lead to residual effects.

A reasonable duration of action is needed if frequent awakenings during the night are the main feature of the insomnia, and flurazepam and nitrazepam have been used for many years in this context. Low doses of these drugs should be used, but, even if residual effects the next day are avoided, accumulation will occur with repeated ingestion. Sustaining sleep without residual effects and without accumulation on nightly ingestion is more likely to be achieved with the newer generation of rapidly (as opposed to ultrarapidly) eliminated hypnotics, such as brotizolam and zopiclone, because their rates of elimination are still sufficiently fast for an appropriate dose to be free of residual sequelae.

It would appear that sustaining sleep without residual effects the next day requires a drug which is adequately absorbed (peak plasma level reached within an hour after ingestion) or in which the elimination phase demonstrates the fall in plasma concentration with a mean half life of around 5 hours. Ultrarapidly eliminated hypnotics with mean elimination half-lives between 2 and 3 hours and hypnotics with a marked distribution phase are more appropriate when there is difficulty falling asleep. With these drugs doses higher than those required to initiate sleep are needed to sustain sleep. Such high doses should be avoided as they may lead to high plasma concentrations during the early part of the night which could be accompanied by respiratory depression, alteration of sleep architecture, residual effects including anterograde amnesia, and rebound insomnia on cessation of continued therapy.

The question of adverse effects of benzodiazepines arises frequently, but there is no convincing evidence that these are unavoidable. Unnecessarily high doses for unnecessarily long periods are the main causes, and adverse effects may imply misuse. Adverse effects include impaired performance the next day and anterograde amnesia, and such sequelae are, of course, of significance to certain occupations. Impaired performance the next day is largely related to dose and pharmacokinetic profile, and so the correct dose of the appropriate drug is essential.

Insomnia on cessation of treatment may also be a sequel to the misuse of hypnotics as rebound phenomena are a feature of many drugs if they are withdrawn suddenly. With rapidly eliminated hypnotics insomnia tends to occur during the first night or so after withdrawal, but with slowly eliminated drugs the fall in plasma concentration after withdrawal is relatively slow and sleep disturbance is unlikely to occur. Rebound insomnia occurs when relatively high doses of rapidly eliminated drugs are used nightly for several weeks. It is not observed when these drugs are used in appropriate doses for a limited period. Dependency is also a possibility with the use of hypnotics. It can be minimised by the intermittent use of low doses together with limited duration of ingestion, and gradual withdrawal in the event that continued treatment has been given for more than a month. Dependency is unlikely to present as a problem with hypnotics if they are used judiciously.

CHAPTER 5

DISTURBED SLEEP

Disturbed sleep over a day or two may arise from a change in surroundings or from difficulty in coping with an unusual pattern of work, and it is in this context that aircrew may present with sleep difficulties. Indeed, changes in their sleeping environment, and rest at unusual times are for many aircrew part of their day to day life. Even limited alterations disturb some individuals — particularly if they occur suddenly. Similarly, work by day and rest by night are in harmony with the normal pattern of sleep and wakefulness, and those who work unusual hours and have to cope with time zone changes are likely to be out of phase with this natural rhythm. In this chapter we deal with the two main circumstances which may lead to sleep disturbance in aircrew — shiftwork and transmeridian flights.

SHIFTWORK

Shiftwork is required for a variety of reasons, and economic considerations have played an important part in the increase of this activity. In industrialised countries around 20% of the workforce are engaged in shiftwork. When we work by day and rest at night the circadian variations in our physiological and psychological functions are in harmony with this routine, but in shiftworkers rest and activity patterns are out of phase with environmental synchronisers. A single night shift does not change the circadian rhythm of body temperature. Consecutive night work for at least seven days is required to shift the time of minimum temperature to a point within the new sleeping period, though it is not clear whether other physiological functions re-entrain at the same rate.

The extent and significance of dysynchrony in shiftworkers depends on the individual as well as the work-rest pattern. Some shift systems include weekends and in these abnormal rest and activity patterns may be a continuous feature. Disturbed sleep is one of the major consequences of shiftwork. The night worker is forced to rest during the day when environmental factors do not favour sleep. Light and noise levels are higher than at night, and these changes may be more easily appreciated during the light sleep of the day. There are also higher ambient temperatures and social influences which may disturb even the most tired morning sleeper.

Indeed in a group of workers who slept nearly 8 hours at night, only about $5\frac{1}{2}$ hours sleep was obtained during the day. With morning sleepers the later they retire the less they may sleep. It is estimated that more than 50% of shiftworkers suffer from sleep disturbance, whereas in dayworkers the figure is between 5 and 20%.

The temperature cycle may influence the ability to maintain daytime sleep. There is a tendency to wake up just before the peak in body temperature, and studies in isolated environments have suggested that when body temperature is low, the probability that one will sleep is high and vice versa. The duration of sleep may therefore depend on the position of the sleep period within the temperature cycle. The amount of adrenaline and noradrenaline excreted during daytime sleep correlates negatively with total sleep time and positively with sleep latency and the number of stage changes.

Sleep length related to morning shiftwork is close to that obtained by those on a night shift, and this suggests that it may not only be the night shift which causes difficulties. Sleep before an early morning shift will be curtailed because of the schedule, and workers may be unable to compensate by starting their sleep earlier, near their alertness peak. The length of a sleep period after night shiftwork is shortened because the individual is unable to stay asleep.

It is not only the length of sleep that is important, but also its "quality". Sleep after a nightshift usually contains less stage 2 and REM sleep, sometimes slow wave sleep and sleep efficiency may also be reduced although this does not generally occur. Although REM sleep may be reduced its first occurrence in the sleep period may be earlier than at night. Shiftworkers often compensate for lost sleep by napping and extending sleep during days off.

Although the physiological disturbances associated with shiftwork have been studied in detail, social difficulties are probably more important for the shiftworkers themselves. It may be possible to plan shift systems which minimise physiological disturbances, but these may not be acceptable as they may involve undue disruption of family and social life. Surveyed shift workers rated the effects of their work on their social life to be more important than irregular sleeping times. Indeed in the design of schedules, social needs as well as physiological considerations must be taken into account.

Rhythms of body temperature and simple performance follow a similar pattern over a 24 hour period, with a minimum in the early morning hours. Therefore, when night work involves "simple tasks", performance during a night shift may be worse than during a day shift, whereas this may not be the case for more complex tasks. Efficiency tends to follow this pattern and during two weeks of consecutive night work gradually changes from a pronounced within shift decrement to a relatively constant level of performance. In general, memory loaded performance rhythms seem to adjust more quickly than others to changes in the sleep-wakefulness cycle.

However, considerable individual differences between subjects exist. Temperature and "simple" performance curves vary in phase and according to whether the individual is a morning type or an evening type as defined by questionnaires. This may have implications for selection. Further, some subjects are able to carry out shiftwork throughout their working lives without problem, whereas others suffer from fatigue and sleep disturbance as well as other symptoms such as gastrointestinal disorders after several years, or even after several months. At present it is not possible to forecast whether or not a subject is likely to tolerate shiftwork easily for many years. However, it has recently been suggested that a good tolerance to shiftwork is associated with large amplitude circadian rhythms and a slow adjustment to altered schedules. This does not imply that the natural circadian amplitudes differ between tolerant and non-tolerant shiftworkers — indeed under normal conditions the amplitudes of the poor shiftworker may be within the usually accepted range. It would appear that it is the response of the circadian system to altered work patterns which differs. If this is true, schedules that do not allow the subject's temperature rhythm to adjust to a new "synchronisation" would appear to be preferable, and this would imply that a rapid rotation (change every 2 — 4 days) is a better choice than weekly rotation.

Older people may have difficulty in adapting to shiftwork. Total sleep requirement decreases although more naps may be taken. Furthermore, those over 50 years of age are generally less flexible, both physiologically and socially than young people. Indeed a major predictor of sleep length and sleep quality in those who work at night is the age of the worker — increasing age being associated with more problems. On the other hand this relation may be reversed for early morning work, and so a general difficulty in shift working is not related to aging. Indeed, this suggests that age related changes in circadian rhythms may be involved. "Morningness" may increase with age with earlier peaks in temperature and activity rhythms. It is also possible that internal desynchronisation of the circadian system becomes more likely with increasing age, making the individual more susceptible to disturbances of the sleep-wakefulness cycle. In experienced workers problems with the night shift may appear around 45 years of age.

Although it is not possible to design a single system which is optimal for all shift workers and for all working conditions, certain criteria should be considered. Since the endogenous free running period of the sleep wake cycle averages 25 hours, schedules which involve phase delay are preferable to those that involve phase advance. However, in practice phase delay schedules are rarely operated. Most workers prefer the increased 'time off' intrinsic in a phase advanced schedule. Further, it is true that working for more than seven nights allows re-entrainment and where possible this may be desirable, however, for social reasons most workers prefer a change of shift or rest days after no more than one week. Re-entrainment is therefore not normally possible. At least 24 hours of free time is desirable after each night shift. Sleep disturbances and reduced sleep duration are common complaints, and accumulated sleep deficit over several days should be avoided. To prevent sleep deprivation, a substantial recovery period is desirable. Similar problems may arise with early morning workers. In this case a 24 hour rest is also beneficial, though reorganisation of the shift system with later starting times would be an alternative solution.

The length of the shift should be related to the type of work. With light work the shift duration may be extended to 12 h, but it should not exceed 8 h, or even 6 h, when heavy physical expenditure or a high mental workload is involved. The cycle of the shift system should not be too long (ie 4 weeks is better than 40 weeks), and a regular system of rotation is preferable to an irregular one. Short cycles and regular systems make it easier for the worker and his family to arrange their social life. In the case of continued shiftwork, it is important to arrange as many free weekends as possible so that a reasonably normal social life is possible.

Because shiftwork cannot be tolerated by about 20% of the working population, selection is important. It is not yet possible to give definite criteria, but shiftwork is contraindicated for some groups. New employees living alone, those under 25, and those over 50 years of age should be carefully monitored, though experienced, well adapted individuals can in many cases remain in shiftwork beyond the age of 50. A history of digestive tract disorders may lead to problems which may be exacerbated by unusual times of meals or to increased caffeine intake and smoking, both of which are common in nightworkers. Patients with diabetes and thyrotoxicosis may also find it difficult to ensure regular food and correct timing of medication and the incidence of fits in epileptics may be increased by sleep reduction.

Some irregularity of sleep is inherent in most air operations. In short-haul routes duty hours may encroach on the normal nocturnal sleep period, and some periods may be shortened. The mean duration of sleeps over several months may be similar to that observed in normal day-to-day activities (7.6 hours) but the range is much greater (5 hours to more than 9 hours). This would appear to be the adaptation of the short-haul pilot to duty hours which encroach on early morning and, perhaps, late evening sleep. Naps are not usually a feature of the sleep of the short-haul pilot: prolongation of some sleep periods is the essential compensation and may involve many months of the year.

TRANSMERIDIAN FLIGHTS

The disturbance of sleep which occurs when individuals have to cope with time zone change is of particular importance to the practice of aviation medicine. Transmeridian flights involve journeys across latitudes and produce rapid and often large displacements which desynchronise biological rhythms from those of the environment. Subjectively most complain of tiredness, loss of appetite and a general feeling of loss of well-being, while sleep and wakefulness occur at unusual times. Desynchronisation of rhythms may lead to changed levels of performance at certain times of the day, while the ensuing need to synchronise rhythms to a new time zone leads to sleep difficulties. Sleep after transmeridian flights is influenced by a variety of factors including the timing of the flight and subsequent displacement of rest periods due to the direction of travel.

After westward flights across the North Atlantic involving a delay of 5 to 6 hours to the first rest period, individuals tend to fall asleep quickly and sleep more deeply. Some degree of sleep deprivation is involved in this phenomenon, but falling asleep quickly may also be related to the lateness of going to bed which is

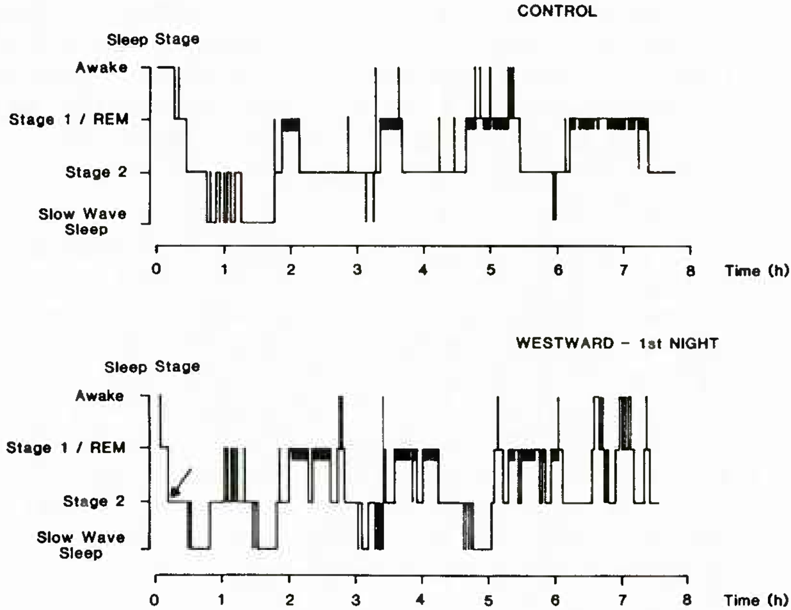

Fig.25 Hypnograms in a young adult before and after a 5 h westward flight.

well into the night of the natural rhythm for sleep and wakefulness. However, there tends to be less restful sleep during the latter part of the night as individuals try to sleep toward the local time of rising which is around midday in the home time zone (Figure 25). The delayed rest period is also likely to modify sleep in other ways. There may be an increase in REM sleep as REM activity is likely to be greatest when individuals sleep later in their rhythm of sleep and wakefulness. By the third night normal sleep patterns are usually well established, and this indicates, together with the realignment of the rising phase of alertness in the daytime sleep latencies, that the individual, at least as far as his sleep-wakefulness continuum is concerned, has adapted to the new time zone.

Sleep during the first night after an overnight eastward journey across the north Atlantic in which the first rest period may be delayed by 19 hours may be even better than before the flight if the subjects do not sleep on the aircraft or during the first day in the new time zone. In the new time zone with a relatively early sleep period, sleep onset is delayed and there is likely to be a reduction in REM sleep. There is, however, an interesting development some days after an eastward flight. Slow wave sleep and total sleep time are shorter and sleep efficiency is reduced, and these changes, together with the slow realignment of the rising phase of the daytime sleep latencies, show that the sleep-wakefulness continuum may not relate to local time for several days after an eastward flight (Figure 26).

How are these differences between eastward and westward flights intepreted? A reasonable explanation is that our innate circadian rhythmicity is longer than that of the day-night cycle, and that without the influence of the environment we have a natural desire to lengthen our day. This is the tendency after a westward flight with its delay to sleep, but after an eastward flight we have to shorten our day and it is possible that, here, there is an inherent resistance. Some individuals may even prefer to lengthen their day after eastward shifts, but the extent to which this occurs is unknown, though equally it may lead to persistent sleep disturbance.

With aircrew the main problem with transmeridian flights is coping with, rather than adapting to the time zone (Figure 27). After a westward flight crews usually sleep well, even though sleep may be somewhat disturbed in the latter half of the night. It is the timing of the return flight which is important — particularly if it is overnight. A significant shift of the circadian rhythm to the new local time will have taken place if the crew have stayed in the new zone for a couple of days, and the rising phase of alertness will now be displaced from that normally observed in the home time zone, but still earlier than that usually observed in the new time zone. During the day of the return flight this will mean that they will be less alert than appropriate during the late afternoon and early evening. With a time zone change of 8 hours a late departure around 6 o'clock would allow the crews to take a nap in the afternoon, and the advance in the rising phase of alertness in the home time zone would increase alertness during the latter part of the flight terminating during the early morning.

Some aircrew are involved in repeated crossing of time zones or in north-south operations which involve night flights. In these circumstances their sleep becomes irregular over several days. The sleep of a pilot operating an eastward round-the-world schedule is illustrated in Figure 28. It is read from the bottom line up, and each line is from midday of one day to midday of the next, and each

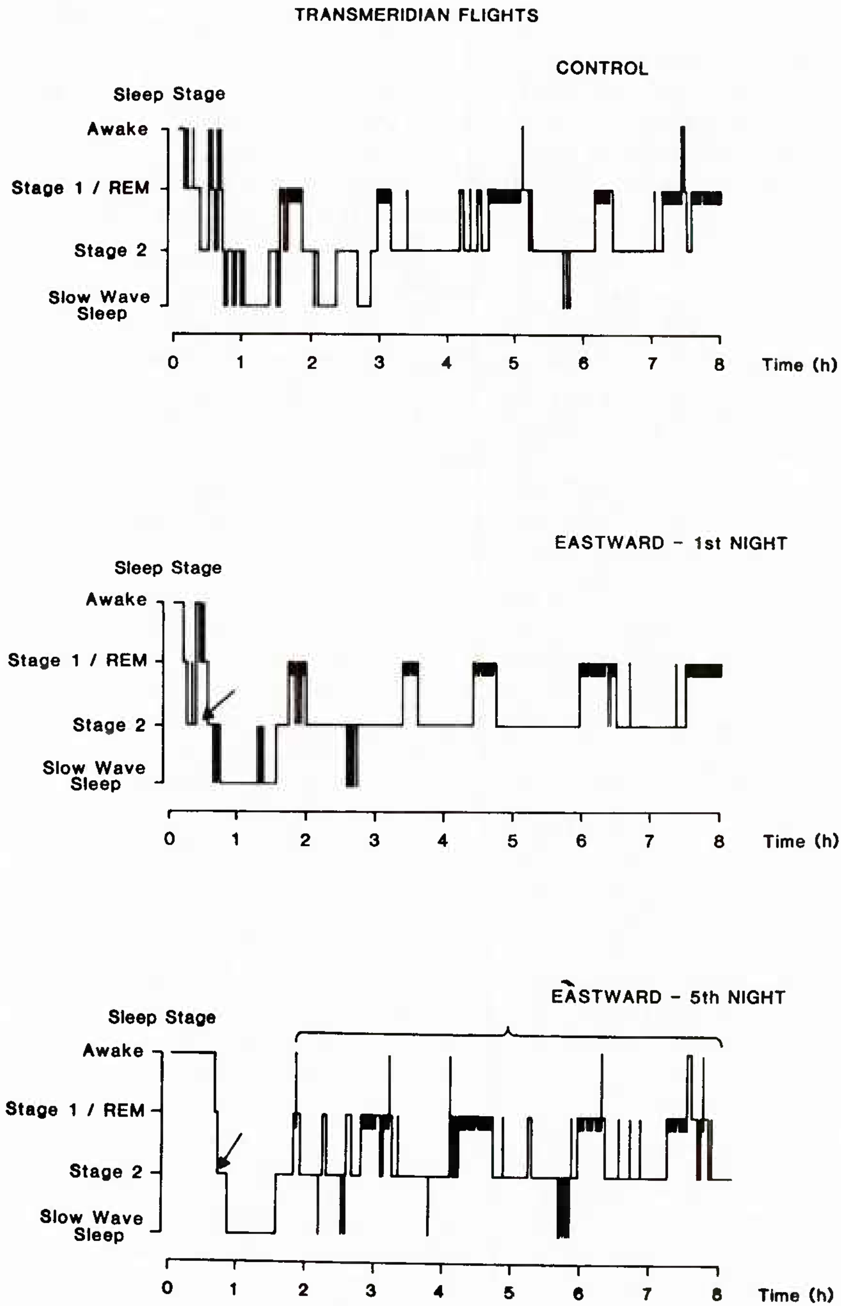

Fig.26 Hypnograms in a young adult before and after a 5 h eastward flight.

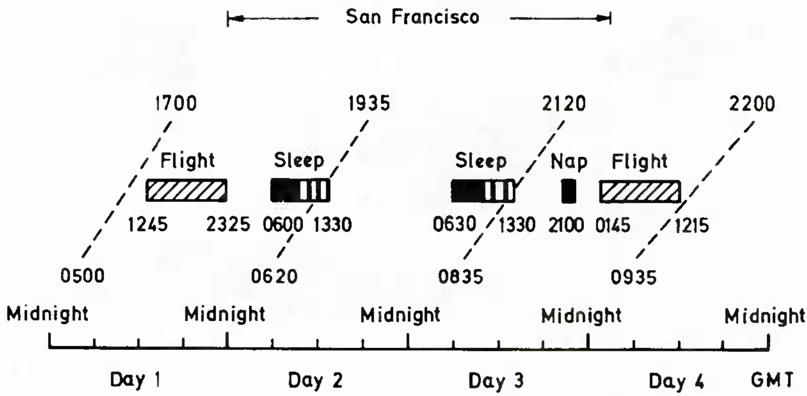

Fig.27 Importance of the timing of an eastward flight after a westward time zone change of 8 h. The scheduled departure time of the flight from London was 1245 h (GMT) and it landed in San Francisco at 2325 h (GMT) which was nearly 4 o'clock local time. The aircrew went to bed about 10 o'clock local time (0600 h GMT the next day), and stayed in bed until nearly 6 o'clock the next morning (1330 h GMT). They slept at about the same time the next night. Sleep may have been less restful than usual during the latter part of each local night, but it was nevertheless satisfactory. Arrangements preceding the return flight were of prime importance as the flight was overnight, and followed several days of potential sleep disturbance. Departure time was nearly 6 o'clock (0145 h GMT the next day), and the crew took a nap during the afternoon. The timing of the return flight was critical for another reason. The aircraft arrived in London at 1245 h GMT, and though the rising phase of alertness during the day (dotted lines with minimum and maximum values at times indicated) after the overnight return flight would have been somewhat later than usual due to the shift of about 4 h towards San Francisco time, it nevertheless would have increased alertness during the latter part of the flight.

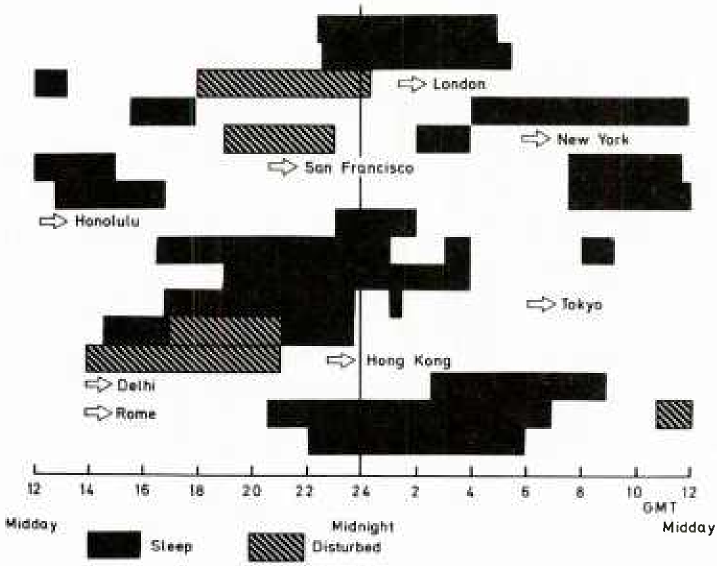

Fig.28 Irregularity of sleep during an eastward round-the-world schedule.

rectangle is a period of sleep. Hatched rectangles indicate subjectively poor sleep. The irregularity of sleep both with respect to duration and time of day is evident. Indeed, the dominant feature of the sleep of aircrew who operate world-wide routes is irregularity both in terms of duration of sleep and of time of day when it occurs.

The sleep of pilots operating worldwide east-west routes has received much attention. With 24-hour rest periods a long sleep immediately after a flight could mean that the crew would not be in the most rested state possible for the next duty, and so, to avoid undue sleepiness during duty after a 24-hour rest, crews often split their sleep into two parts. The need for sleep immediately before duty is ensured by restricting sleep immediately after the preceding flight. This often leads to sleep periods of 3 — 4 hours during long-haul schedules. During flights which extend wakefulness beyond 16 hours and flights which start during the early evening, naps of ½ — 1 hour duration are not uncommon, and they probably assist in the adaptation to new time zones, particularly on westward flights when the day is lengthened. In this way the sleeps of long-haul crews may range from ½ hour to ½ day in length (Figure 29).

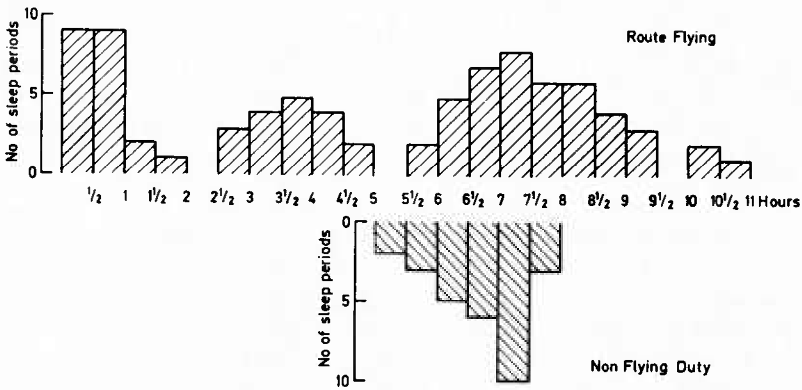

Fig.29 Incidence of sleeps of various durations during a month of flying duty and during a month of non-flying duty.

CHAPTER 6

TRANSPORT OPERATIONS

The management of aircrew coping with irregularity of rest and activity is complicated though, without doubt, the key is in the design of duty schedules. Long range operations incompatible with acceptable sleep or heavy short range schedules over many months could prejudice safety, and so duty hours are of legitimate interest to the practice of aviation medicine. Normally, workloads must allow crews to achieve an acceptable sleep pattern, and the scheduling of duty must avoid marked falls in performance due to an adverse juxtaposition of prolonged duty with the nadir of circadian performance. These are the two most important considerations, and in this way arrangement of the hours of duty provides the foundation of effective management.

There is a cumulative effect of irregular work, and a critical factor in achieving sleep is the limit to duty hours over any number of days. A small increase in hours may convert an acceptable to an unacceptable schedule, and so a small reduction in the overall number of duty hours may have a particularly beneficial effect. Such a modification may allow an additional period of sleep within a schedule of many days or provide greater flexibility in the choice of time to sleep during a particular rest period. It is, of course, difficult to create ideal schedules, but, with care, reasonably satisfactory ones can be designed to include the facility to hasten operations, and to cope with the extra workload which minor changes in crew availability can create.

Duty hours compatible with sleep do not increase linearly with the number of days of the schedule. Indeed, there is some evidence that the rate of increase falls off due to the cumulative effect of the irregularity of sleep (Figure 30). Aircrew operating world-wide routes are able to cope with 50 — 55 hours duty in the first 7 days of a complex schedule, but they can only manage about 75 hours by the end of 14 days. This effect should be considered in the scheduling of aircrew as rate of working is the basis of any system of flight time limitations (Tables I and II).

Avoiding undue sleep disturbance is of prime importance, but the characteristics of a particular period of work could adversely influence effectiveness. This is a possibility when individuals are

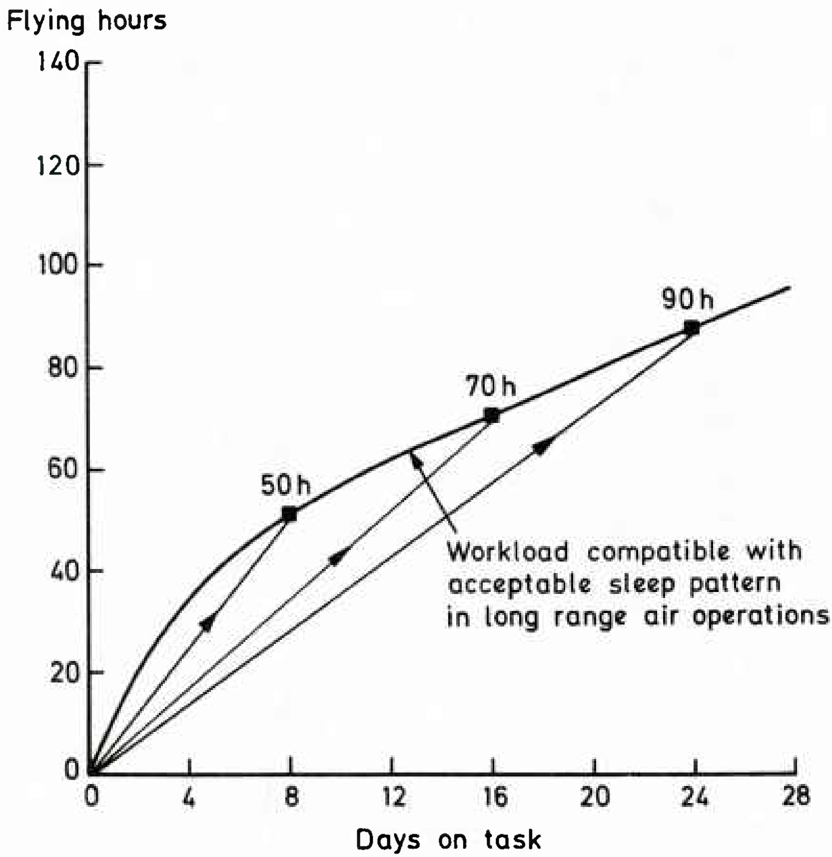

Fig.30 Duty hours related to time on route believed to be compatible with an acceptable sleep pattern.

expected to be continuously on task for long periods of time — as in two crew operations. In these circumstances it is important that the durations and timing of duty periods should not adversely affect the ability to sustain vigilance. Several factors influence sustained performance. They are the interval between the end of the previous sleep and the commencement of duty (time since sleep), duration of duty (time on task), and, assuming they are adjusted to the local time zone, the clock time of duty (time of day).

TABLE I

Duty Hours within Schedules of Defined Length of Optimum and Maximum Workloads

Days on route	*Duty hours*	
	Optimum workload	*Maximum workload*
2.0	26	29½
3.0	32	36
4.0	37½	42
5.0	42	47
6.0	46	51
7.0	50½	55
8.0	54	58½
9.0	57	62
10.0	60½	65
11.0	63½	68
12.0	66½	71
13.0	70	74
14.0	73	76½
15.0	76	79
16.0	79	82

TABLE II

Duration of Schedules for Total Duty Hours at Optimum and Maximum Workloads
Proposed Duration of Schedule (hours)

Total duty hours	*Optimum workload*	*Maximum workload*
30	64	—
40	109	88
50	165	138
60	237	202
70	312	280
80	—	368

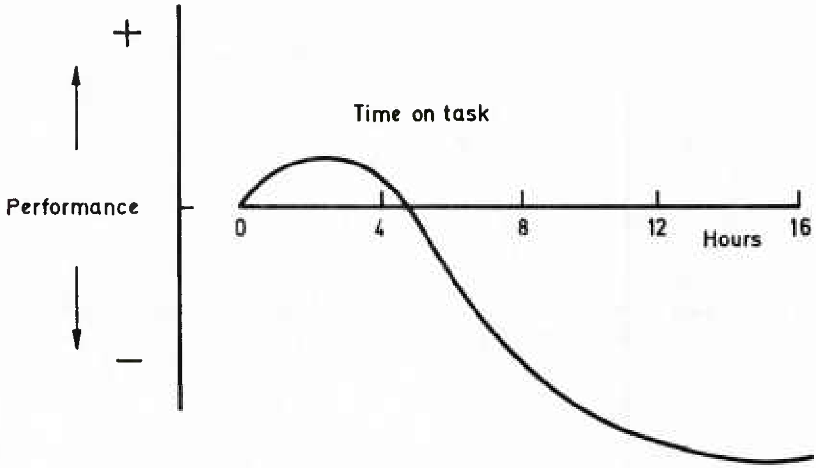

Fig.31 A model of change in performance with time on task.

As far as "time on task" is concerned performance is likely to rise during the first few hours, and fall to its initial value after around 5 hours, and level off around 12 to 16 hours after commencement of duty (Figure 31). As far as "time of day" is concerned performance rises during the day and falls during the late evening and overnight to reach its nadir around 0500 hours in the morning (Figure 32). Very low levels of performance would be reached if the latter part of a prolonged duty period coincided with the circadian trough in performance (Figure 33). For example, if a 16 hour duty period commences around 0200 hours it is likely that performance will be maintained as the fall during the latter half of the work period coincides with the rising phase during the day. On the other hand if duty commences around 1400 hours the drop in performance during the latter part of the duty period would coincide with the circadian fall during the night, and so low levels may be reached (Figure 34).

There are, therefore, two overriding concerns in the design of schedules for aircrew. Over several days aircrew must be able to achieve acceptable sleep and this is related to their rate of working. Further, the arrangement of their work must avoid low levels of performance related to the end of a prolonged duty period coinciding with certain times of their circadian rhythm. Careful consideration must be given to the interaction of length of duty and

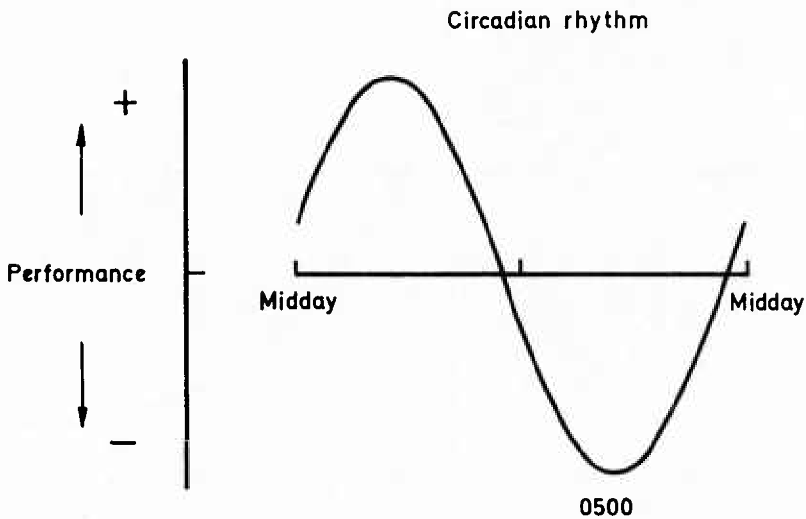

Fig.33 Time on task and time of day related to duty commencing at 0200 and 1400 h.

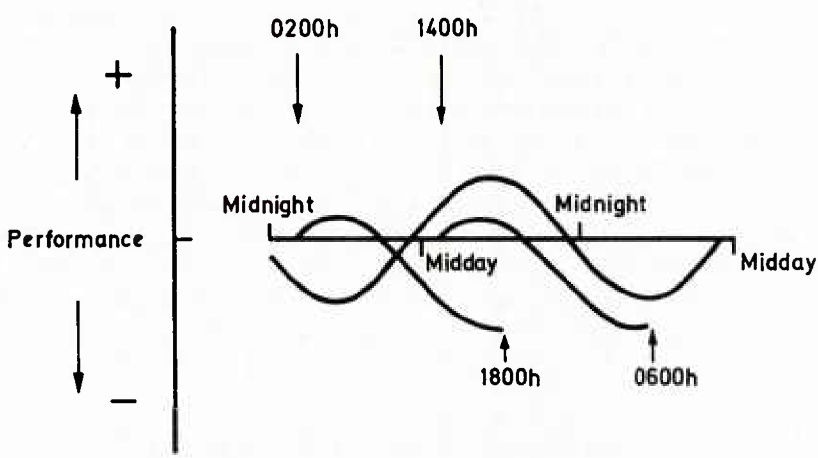

Fig.32 A model of change in performance with time of day.

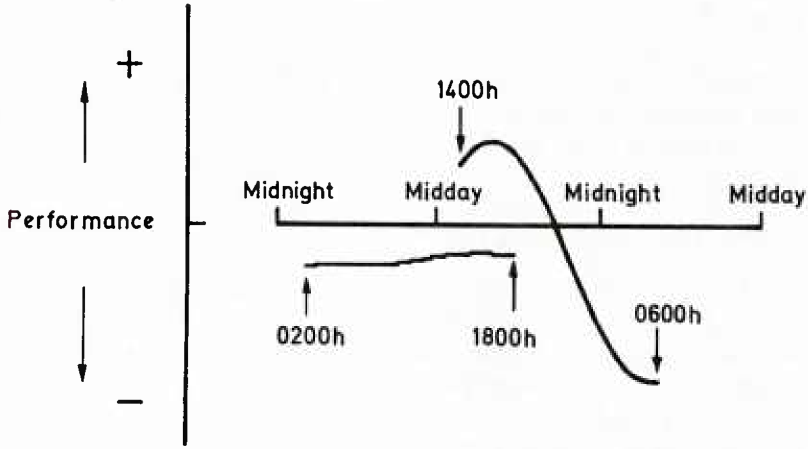

Fig.34 Resultant of the time on task and time of day related to duty commencing at 0200 and 1400 h. If a 16 h duty period commenced around 0200 h it is likely that performance would be maintained as the fall in performance during the latter half of the work period would coincide with the rising phase during the day. On the other hand if the duty period commences around 1400 h the fall in performance during the latter part of the duty period would coincide with the lowest level during the night related to the circadian rhythmicity of the individual, and so very low levels of performance may be reached. Such adverse juxtapositions of time on task and time of day should be avoided if crews are expected to remain continuously on their task. For this reason careful attention must be given to the length of duty periods in such operations, and the length should be determined in relation to the time of day. These considerations assume that the aircrew are fully rested at the commencement of their duty.

time of day. In this context, therefore, we cannot predict with complete accuracy the rate of adaptation of the circadian rhythm to the local time of the new time zone, but some approximations can be made which will avoid serious adverse juxtaposition of time on task and time of day.

In coping with irregularity of work short periods of sleep seem to be very useful. However, it would appear that though naps of about an hour may decrease the tendency to sleep, they have a limited beneficial effect on performance when an individual has become tired as when working overnight. Naps may improve performance, but this would appear to be limited when deterioration in performance has settled in. On the other hand, periods of sleep of about 4 hours in the evening before long periods of work overnight work appear to be very useful and to lead to a sustained improvement in performance overnight. This would suggest that performance overnight can be more easily sustained by a preceding sleep of several hours than by attempting to overcome the effects of sleep loss by naps.

CLINICAL CONSIDERATIONS

However, even taking into consideration all these points some aircrew still find it difficult to cope with irregularity of rest, and this is particularly likely in middle age when sleep begins to deteriorate. Irregularity of rest superimposed upon poor sleep can be troublesome, and a careful assessment should always be made if aircrew complain of persistent and unusual difficulty in coping with their work. It must be remembered that persistent sleep disturbance could reflect illness. A history over many months raises the question whether the patient is suffering from one of the many causes of chronic insomnia and depression. Unwise use of alcohol or drugs are also possibilities, while a more recent history in the absence of illness may suggest personal difficulties, either with the family or at work.

The normal deterioration in sleep may be exaggerated with repeated arousals due to an unusual frequency of apnoeas and leg movements, and, though such events in themselves may have limited or no clinical significance, they could indicate a developing sleep apnoea syndrome or be a manifestation of the restless legs syndrome. Excessive daytime sleepiness as well as disturbance of sleep are often seen in these conditions, and such sleep problems may not be compatible with air operations. In the case of the sleep apnoea syndrome there may be other problems such as hypertension.

If the practitioner is satisfied that there is no medical or psychological background to the complaint the initial approach is to counsel the individual to look after his sleep. Exercise and avoiding heavy meals may help and limiting the use of alcohol and caffeine may also be of benefit. Changing to less demanding routes is also a possibility. Persistence of the complaint after attention to sleep habits and to the nature of the work suggests that hypnotics may be used. Certainly, there is unequivocal evidence of disturbed sleep in air operations, and for this reason the use of hypnotics at specific points in the schedule is warranted, but choice must relate to the nature of the insomnia and to the lifestyle of the patient. The prescribed hypnotic must be appropriate to the work of the airline pilot, and this means that normal sleep architecture, both during ingestion and after withdrawal, must be preserved, and that the drug must be free from unwanted effects on daytime function.

Experience in the United Kingdom has led to temazepam (10 to 20 mg) being the drug of choice for aircrew when operating a schedule. However, it is important that the rapidly absorbed formulation is used (Normison-Wyeth). Temazepam has a relatively short duration of action due to adequate absorption and marked distribution, and its rate of elimination is such that accumulation does not occur on repeated ingestion. Its short duration of action provides an adequate margin of safety. However, sometimes the problem may be that of disturbed sleep after returning home, when a drug with a slightly longer duration of action with the potential to sustain sleep but still free of residual effects, may be more appropriate. At the time of writing (January 1987) brotizolam (0.125 — 0.25 mg — Boehringer Ingelheim) is the only one available and then only in the Federal Republic of Germany, Holland, Belgium and Ireland. An alternative, though slowly absorbed, is oxazepam (15 — 30 mg), while a drug with a similar pharmacokinetic profile, zopiclone (5 mg — May & Baker), is under development. The characteristics of currently available hypnotics and those under development are reviewed in Table III.

In any event, the practitioner should prescribe an hypnotic with which the individual is familiar, and the drug should be tested "on the ground". It should be given, initially, at the lowest dose and then as infrequently as possible. The practitioner should help to identify when its use is likely to be most beneficial. With the use of temazepam during the schedule there should be an interval of 24 hours between ingestion and commencement of duty, though under medical supervision the interval may be reduced to 12 hours. Perhaps it is unnecessary to emphasise that, if hypnotics are to be used in the management of sleep disturbances in aircrew, the concomitant use of alcohol should be discouraged and preferably avoided.

There is now a well defined approach to the management of aircrew who have to cope with irregularity of work. Their pattern of work and of rest is largely determined by flight time limitations, and so it is appropriate that expertise in aviation medicine is brought to bear on the formulation of such guidelines. However, the day to day

TABLE III Pharmacokinetic Properties of Some Currently Available Hypnotic Drugs

Significant pharmacokinetic characteristics	*Drug (chemical group)*	*Recommended dose range (mg)*	t_{max} *(hours)*	$t_{1/2\beta}$ *(hours)*	*Comments/indications*
Slow absorption	Loprazolam mesylate (midazobenzodiazepine)	1.0—2.0* (elderly up to 1.0)	5.0 ± 3.6	8.0 ± 3.4	Slow and variable absorption with persistent effects the next day. Precise clinical indication uncertain. *Doses exceeding 1.0 mg lead to residual effects.
	Oxazepam (benzodiazepine)	15—20 (elderly 10—20)	2.2 ± 1.0	7.8 ± 1.7	Free of residual effects, but rather slowly absorbed. Used mainly as an anxiolytic, but also sustains sleep.
Slow elimination of parent compound or metabolite.	Flurazepam hydrochloride (benzodiazepine)	15—30* (elderly 15 mg)	1.4 ± 0.7	1.0 ± 0.1	Hypnotic effect related to the activity of both metabolites. Residual effects likely, and accumulation on continued nightly ingestion inevitable. Useful for frequent nocturnal awakenings when some daytime sedation acceptable. 7.5 mg may be useful for the elderly. *Doses exceeding 15 mg may not be appropriate.
	Active metabolites: 1-hydroxyethylflurazepam desalkylflurazepam		8.0 ± 8.0	40—103	
	Clorazepate potassium (benzodiazepine)	15.0—22.5 (elderly 7.5—15.0)			Slowly eliminated metabolite (desmethyldiazepam) has hypnotic activity and provides steady anxiolytic effect the next day with little, if any, sedation or impaired performance. Useful for insomia when anxiety is a feature.
	Active metabolite: desmethyldiazepam		0.9 ± 0.3	63.7 ± 9.5	

Relatively slow elimination, but marked distribution may lead to a short duration of action.	Diazepam (benzodiazepine)	5—10 (elderly 0.25—0.5)	1.1 ± 0.3	32.0 ± 11.0	Free of residual effects when given occasionally due to marked distribution phase. Slow elimination of parent compound and active metabolite (desmethyldiazepam) leads to accumulation and daytime anxiolytic effect with repeated ingestion.
	Flunitrazepam (benzodiazepine)	0.5—1.0* (elderly 0.5)	1.0 ± 0.5	15.5 ± 4.8	Rapidly absorbed with marked distribution phase, but relatively slow elimination. Low dose (0.5 mg) for sleep onset. Doses exceeding 1.0 mg used in some countries, but even 1.0 mg likely to lead to some residual effects and accumulation on daily ingestion. *Doses exceeding 1.0 mg may lead to rebound insomnia.
	Nitrazepam (benzodiazepine)	5—10* (elderly 2.5—5.0)	1.4 ± 1.0	30.0 ± 5.0	Residual effects likely and accumulation on daily ingestion inevitable. Useful for frequent nocturnal awakenings when some daytime sedation acceptable. *Doses exceeding 5 mg may not be appropriate.

TABLE III (Continued)

Significant pharmacokinetic characteristics	*Drug (chemical group)*	*Recommended dose range (mg)*	t_{max} *(hours)*	$t_{1/2\beta}$ *(hours)*	*Comments/indications*
Relatively rapid elimination and marked distribution phase in appropriate formulations.	Lormetazepam soft gelatin capsule tablet (benzodiazepine)	 1.0—2.0* 1.0 (elderly 0.5)	 1.0 ± 0.2 2.4 ± 0.4	 10.3 ± 1.4 8.9 ± 1.0	Soft gelatin capsule formulation for sleep onset. Alternative tablet formulation has relatively slow absorption. *Doses exceeding 1.0 mg may lead to rebound insomnia and may not be appropriate.
	Temazepam soft gelatin capsule hard gelatin capsule (benzodiazepine)	 10—60* (elderly 10—20) 15—30*	 0.8 ± .03 2.2 (0.8—4.0)	 8.4 ± 0.6 12.8 (9.4—23.3)	Soft gelatin capsule formulation (Normison — Wyeth) in the dose range 10—20 mg is free of residual effects and of significant accumulation on daily ingestion. Useful for sleep onset. Alternative hard gelatin capsule formulation also available, but rate of absorption slower. *Doses exceeding 20 mg may not be appropriate.
Rapid elimination	Brotizolam (triazolothienodiazepine)	0.125—0.25 (elderly 0.125)	1.1 ± 1.0	5.1 ± 1.2	Potential to sustain sleep. Free of residual effects and of accumulation on continued nightly ingestion. Available in several European countries (Lendormin — Boehringer).
	Zopiclone (cyclopyrollone)	3.75—7.5 (elderly 3.75)	1.4 ± 0.6	5.3 ± 0.8	Potential to sustain sleep, though 7.5 mg may lead to minimal residual effects in some individuals. Free of accumulation on continued nightly ingestion. Becoming available.

Ultrarapid elimination	Midazolam (imidazobenzodiazepine)	7.5—15.0*	0.3 ± 0.11	1.9 ± 0.4	*Dose range not yet finalised, but 7.5 mg is probably adequate for sleep onset. Doses exceeding 15 mg may lead to rebound insomnia. Under development.
	Triazolam (triazolobenzodiazepine)	0.25* (elderly 0.125)	1.2 ± 0.5	2.6 ± 0.7	Dose range in some countries is 0.25—0.5 mg, but the higher dose leads to residual effects and rebound insomnia. Useful for sleep onset. *0.125 mg may be useful for adults other than the elderly.
	Zolpidem (imidazopyridine)	10	0.5—2.0	1.7 ± 0.1	10—30 mg free of residual effects. Under development.

care of aircrew is firmly in the hands of the aeromedical practitioner, who must be familiar with the work of the airline pilot, understand the rationale behind flight time limitations and be conversant with disorders of sleep. It is important to remember that illness, both physical and psychological, may also lead to sleep difficulties; particularly in middle aged aircrew. Finally, the practitioner must be aware of the clinical pharmacology of hypnotics as this, together with an understanding of the work of aircrew, will ensure that these drugs are used both effectively and judiciously. With such knowledge a confident approach will be presented to aircrew, and only in a few cases will it be necessary to use hypnotics — though useful they may be.

CHAPTER 7

SUSTAINED PERFORMANCE

The ability to sustain performance at high levels of workload is clearly essential to the effectiveness of military aircrew. Continuous vigilance necessary to maintain such effectiveness is influenced by the duration of the preceding period of wakefulness, by the inherent circadian rhythm, and by the need for sleep. Sleep is essential to sustain high levels of vigilance and maintain effectiveness. The adverse effects of sleep loss extending beyond 24 hours are well recognised, but impairment related to less severe degrees of sleep loss or to irregularity of sleep, both of which are particularly relevant to air operations, is equally important.

The aeromedical specialist in a military environment is frequently involved with prolonged work and disturbed sleep. The inevitable result of sleep disruption, deficit or deprivation, associated with prolonged periods of work, is fatigue. As a complaint it probably indicates sleep deficit, and it is likely to be associated with impaired performance. Fatigue is difficult to define. It involves a subjective appreciation of tiredness, momentary lapses of attention and possibly impaired psychomotor performance. If sleep deprivation persists, although overall performance may still be that of a reasonably acceptable level of efficiency, it is likely to be broken by frequent lapses of attention.

Deficits associated with long periods of work may be underestimated and they tend to be disregarded. Subjectively, at least, individuals may be more easily satisfied with lower levels of performance, and errors remain uncorrected — although they may be recognised. Aversion toward a task may be minimised, at least temporarily, if the individual mobilises his resources to complete the problem. Decrements in performance on the primary task can be avoided, but other elements erroneously believed to be less critical, are impaired. Furthermore, the individual may lose flexibility of approach and the ability to perceive or adjust to new aspects of a problem. This would not be detected if only limited aspects of performance were studied.

There are reasons why it may be difficult to accept that sleep loss leads to impaired performance. Tests of performance may not be sensitive to the nature of the deficits which arise, and the effects of sleep loss vary widely. Interest and motivation often decide whether performance will be altered. Interesting tasks with relatively simple motor skills are resistant for periods as long as 60 hours, but routine monotonous tasks show a rapid and severe decrement after 18 hours without sleep. Motivation may counteract some of the sequelae of sleep loss, and this is important in coping with very high workloads of intensive and sustained operations. However, there is a point beyond which the need for sleep will overwhelm even the most motivated subject.

Nevertheless it is well established that vigilance is dependent on adequate sleep, though other factors of performance, less amenable to measurement, are also affected. Indeed, the preservation of "wholeness" or "behavioural integrality", in those who exercise command is equally, if not more, critical to the success of an operation. Changes in mood such as increased hostility and irritability and inability to concentrate, as well as impaired perception and disorientation which are often experienced with only one night's sleep loss, have an importance far beyond those of the loss of discrete and relatively easily measured skills.

The effects of disturbed sleep on performance may be considered in three ways. Total sleep loss is absence of sleep for at least 24 hours, while partial sleep loss is a reduction in the usual amount of sleep over 24 hours. The third category, irregularity of sleep, implies a fragmented pattern of work and rest which is also likely to involve sleep loss. There is overlap between partial sleep loss and irregularity of sleep, but it is useful from an operational aspect to consider them separately. Irregularity of work and of rest rather than a reduction in the duration of nocturnal sleep is the dominant issue in air operations.

Under operational conditions there is always doubt concerning the extent of the sleep loss. It is difficult to avoid very short periods of sleep, and so to be sure that complete deprivation of sleep loss has occurred. Indeed, in experiments involving long periods of wakefulness — say 72 hours, microsleeps and drowsiness readily occur. They become more frequent as the period of attempted wakefulness continues, and if not immediately aroused the individual will rapidly fall asleep. So-called total sleep loss could be the loss of the normal sleep-wakefulness pattern to a continuum of microsleeps and drowsiness. However, there is little evidence that microsleeps ameliorate the impaired performance which arises from sustained wakefulness, or that drowsy sleep, the transition between wakefulness and sleep, preserves performance.

Under field conditions it may be difficult to suppress sleep, and complete absence of sleep has probably only been achieved in laboratory experiments when the electroencephalogram has been monitored continuously. Early studies with total sleep loss did not consistently detect impaired performance — though changes in mood were obvious. However, as the approach to measurement of performance has become more sophisticated, it is now realised that absence or delay in response rather than accuracy are the important effects, and it was in this way that the importance of adequate sleep to sustain performance was established. Sleep deprived subjects can carry out tasks accurately, but their periods of accuracy become brief and infrequent as the deprivation continues. Sleep deprivation leads to brief intermittent lapses in performance which increase in frequency and duration, and so impaired performance involves missed signals and errors of omission. Memory may also be impaired.

Some situations are more sensitive to sleep loss than others. The longer the task the more obvious are the changes. Loss of a night's sleep may have little effect during the first five minutes of a vigilance task, but deterioration will be obvious when the task is extended to fifteen minutes. Total sleep loss of 50 hours impairs vigilance after three minutes, while after 70 hours it is decreased within only two minutes. The loss of one night's sleep impairs the ability to add after ten minutes, whereas additions may be impaired after only six minutes with the loss of two nights' sleep. Increasing the difficulty will make a task more sensitive. When an addition is required every two seconds no change can be established even after two nights' sleep loss, but when the speed of addition is increased to one every 1.25 seconds, effects are usually observed. Loss of sleep for 24 hours impairs the acquisition of information and the recall of newly learned material, and there is a drop below 40% of baseline levels of performance on such tests toward the end of a 48 hour period of continuous work without sleep or naps.

It is unlikely that proficiency on complex and prolonged tasks can be maintained after 20 hours without rest. Long, repetitive and boring tasks, complex tasks, tasks which involve short-term memory, newly acquired skills and those not well practiced are particularly sensitive to sleep deprivation, though self-paced tasks and feedback on performance levels tend to minimise the effect. It is possible that with some skills even shorter periods of wakefulness would lead to impaired performance. There may also be less specific but, even so, equally important sequelae. Susceptibility to disorientation may be increased, scanning ability may be reduced and the ability to read charts may be affected. Perhaps most important of all, judgement and mood will be impaired.

Recovery from continuous sleep deprivation is rapid, and usually reached within 15 hours. After 36 — 48 hours of continuous work without sleep, baseline performance is regained after 12 hours of rest, although mood changes persist. Further, no matter how long the period of wakefulness, there is a dramatic improvement in performance and behaviour after only one night's sleep. Indeed, subjects deprived of four nights' sleep reach high levels of performance immediately after one recovery night, though more sleep is needed to restore performance to baseline level, and adverse mood changes will persist beyond the sleep of a single night.

It is unlikely that the reduction of any particular stage of sleep which may occur with limited sleep loss is specially linked to impaired performance. The factors which influence performance with total sleep loss are likely to be equally relevant to those which occur with partial sleep loss, even though impaired performance is not a consistent sequel. It appears that most subjects function fairly well during restricted sleep schedules, but many of the tests have been used for relatively short periods, and failure to detect impairment is not surprising. Indeed, the loss of only 2.5 hours sleep each night for 2 nights has been shown to impair vigilance the next morning, and so it must be assumed that repeated partial sleep loss will lead to impaired performance.

Irregularity of work and rest over several days is also followed by falling levels of performance. Recent and cumulated sleep loss, together with the circadian fall in performance during the early hours of the morning, combine during high workload schedules involving irregularity of rest to impair ability, as does the length of the duty period itself.

Efficiency upon sudden awakening poses a further problem. Decrements compared with normal day time values are present immediately after being awakened from a normal night's sleep. The later in the night this awakening occurs the greater the impairment becomes. Recovery may be linear for simple, discrete tasks but return to normal working levels may take as long as 20 minutes. Very low performance is encountered on awakening from poor sleep after a stressful period of work which involves sleep loss. More complex tasks require a longer recovery time. The use of alarms does not accelerate recovery, though a few minutes of rest immediately after awakening offsets the decrement of the subsequent performance. Working in a concentrated manner after a sudden awakening may prejudice the capacity to perform effectively, though the decrement in those who have to face such a requirement repeatedly may be less than would be expected.

OPERATIONAL SIGNIFICANCE

There are still difficulties in bringing together the operational relevance of much of the information which is now available on the effects of sleep loss to sustained and intensive air operations. However, it would be unwise to reject the implications of experimental findings, and it is evident that circadian variations in performance would adversely influence capability in operations which involve work at times when the individual is usually asleep. Disruption of the sleep-wakefulness cycle with some sleep loss is likely to be a problem in all air operations which extend beyond a single day, and sleep loss is likely to intensify as the duration of the mission is prolonged.

Although performance depends on complex interactions between task, environment, work schedule and the individual, it will certainly be impaired when the subject becomes sleepy. Impairment may be minimised if the individual can be motivated to remain alert, but impaired performance follows sleep loss, and with irregularity of work the adverse juxtaposition of falling levels in performance around the circadian nadir and the immediate and cumulative effects of sleep loss all combine to impair ability during long duty periods. Impaired performance will involve vigilance and memory, but impaired behaviour of the individual in the sense of "wholeness" may be more important in situations where the effective interaction of individuals under stress is vital.

Careful attention to sleep is all important because impaired performance follows sleep reduction, even though the impairment may not be easy to demonstrate. It is well known that sleep disturbance modifies circadian functions, impairs response to stress and upsets the normal sense of well being, but the measurement of performance is insufficiently sensitive to detect easily many important behavioural changes. This has allowed the myth to grow that disturbed sleep is of limited significance. This is not so. Performance is maintained by greater effort or by concentrating attention on some aspects of the problem for a limited period of time, and interpersonal skills, judgement and decision making are likely to deteriorate even though such deteriorations are difficult to demonstrate.

The management of military aircrew coping with irregularity of rest and activity is problematic. Operations incompatible with acceptable sleep will prejudice effectiveness. Workloads of aircrew normally allow them to achieve sufficient sleep, and the appropriate scheduling of duty can avoid marked falls in performance due to an adverse juxtaposition of prolonged duty with the nadir of circadian performance. But in intensive and sustained air operations such circumstances are unlikely to be encountered, and most if not all will have to cope with sleep disturbance and will experience difficulty. This is particularly likely with middle aged aircrew whose sleep has deteriorated naturally. Coping with irregularity of rest and sleep loss superimposed upon poor sleep is likely to be a major problem and, with the inevitable disturbance of sleep over many days, the use of hypnotics is almost inevitable. However, the drug chosen must be free from unwanted effects on daytime function.

Temazepam (10 to 20 mg) is the drug of choice for military aircrew in the Royal Air Force. However, it is important that the rapidly absorbed formulation is used (Normison-Wyeth). In this formulation temazepam has a relatively short duration of action due to its distribution phase, and its rate of elimination is such that accumulation does not occur on repeated ingestion. Its short duration of action provides an adequate margin of safety, but it is important that aircrew should use a drug with which they are already familiar. Further, it is far better to use an hypnotic to anticipate a demanding situation rather than to cope with an individual who is tired and fatigued. Normally there should be an interval of 24 hours between ingestion and commencement of duty though under military operations the interval can be reduced to 6 hours.

Another potential use of drugs in intensive operations is that of stimulants to maintain vigilance during long periods of duty or during duty periods which occur overnight. The use of stimulants such as dopamine agonists, and serotonin uptake inhibitors is a complex issue and, currently, our knowledge of these drugs is not sufficient to encourage their use in military operations. However, it is recognised that caffeine — an adenosine antagonist — is used widely by aircrew to maintain alertness, and its use over many years provides a measure of support to the safety of the drug. It can lead to tachycardia and diuresis if high doses are used, and it could impair subsequent sleep. There can be little doubt that caffeine maintains wakefulness overnight and preserves vigilance. It is reasonable that caffeine is used to preserve vigilance even under circumstances when sleep between missions has been ensured. However, it is possible that in the not too distant future advances in our knowledge of stimulants will be such that a much more sophisticated approach to maintaining vigilance will be possible.

In conclusion, we now have a better understanding of the management of aircrew who have to cope with the irregularity of work and rest inevitable in intensive and sustained operations: their pattern of work and rest will probably be determined by operational considerations, and so it is unlikely that their work can be modified under such circumstances. Currently, their sleep must be preserved. Rest periods are likely to be scheduled at unusual times of the day and under circumstances which may not be conducive to sleep, and so the use of hypnotics is likely to be inevitable. Indeed, under the high workload of intensive or sustained operations hypnotics during rest periods provide the most valuable approach to maintaining the effectiveness of aircrew.

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